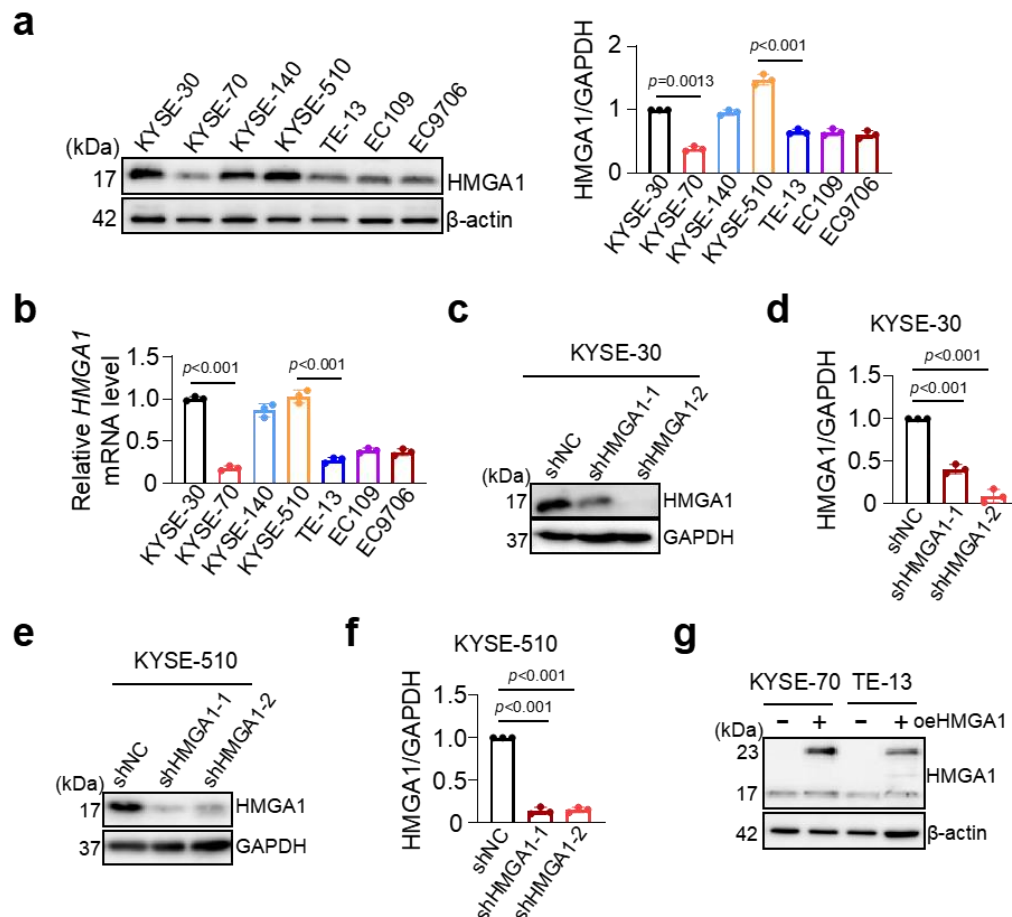
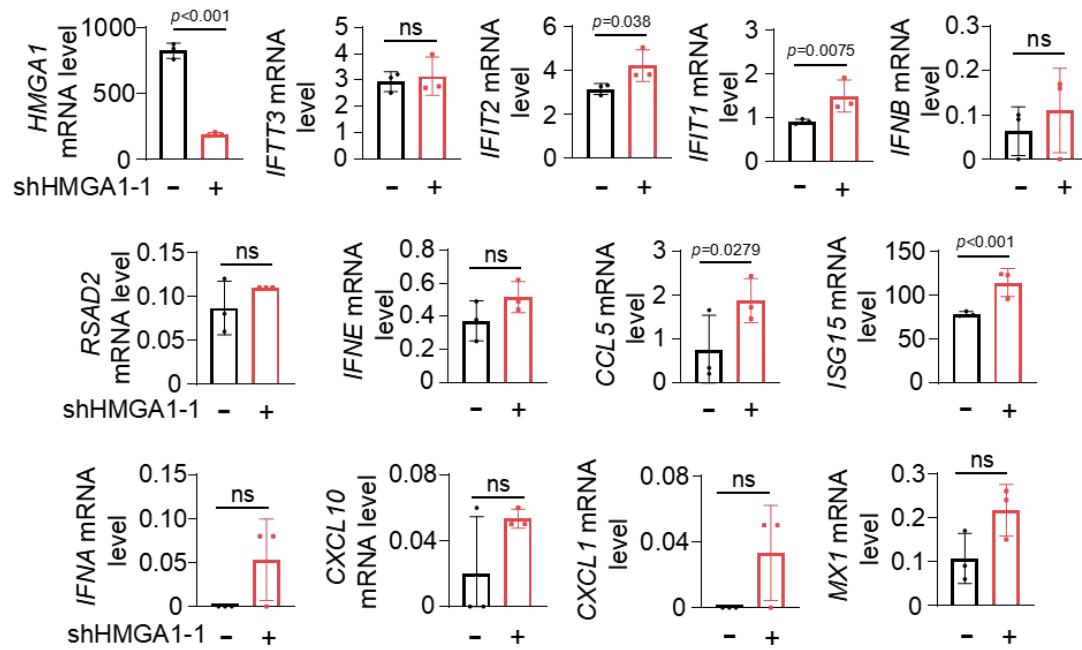


**Supplementary information of “High mobility group A1 (HMGA1) promotes esophageal squamous cell carcinoma progression by inhibiting STING-mediated anti-tumor immunity”**

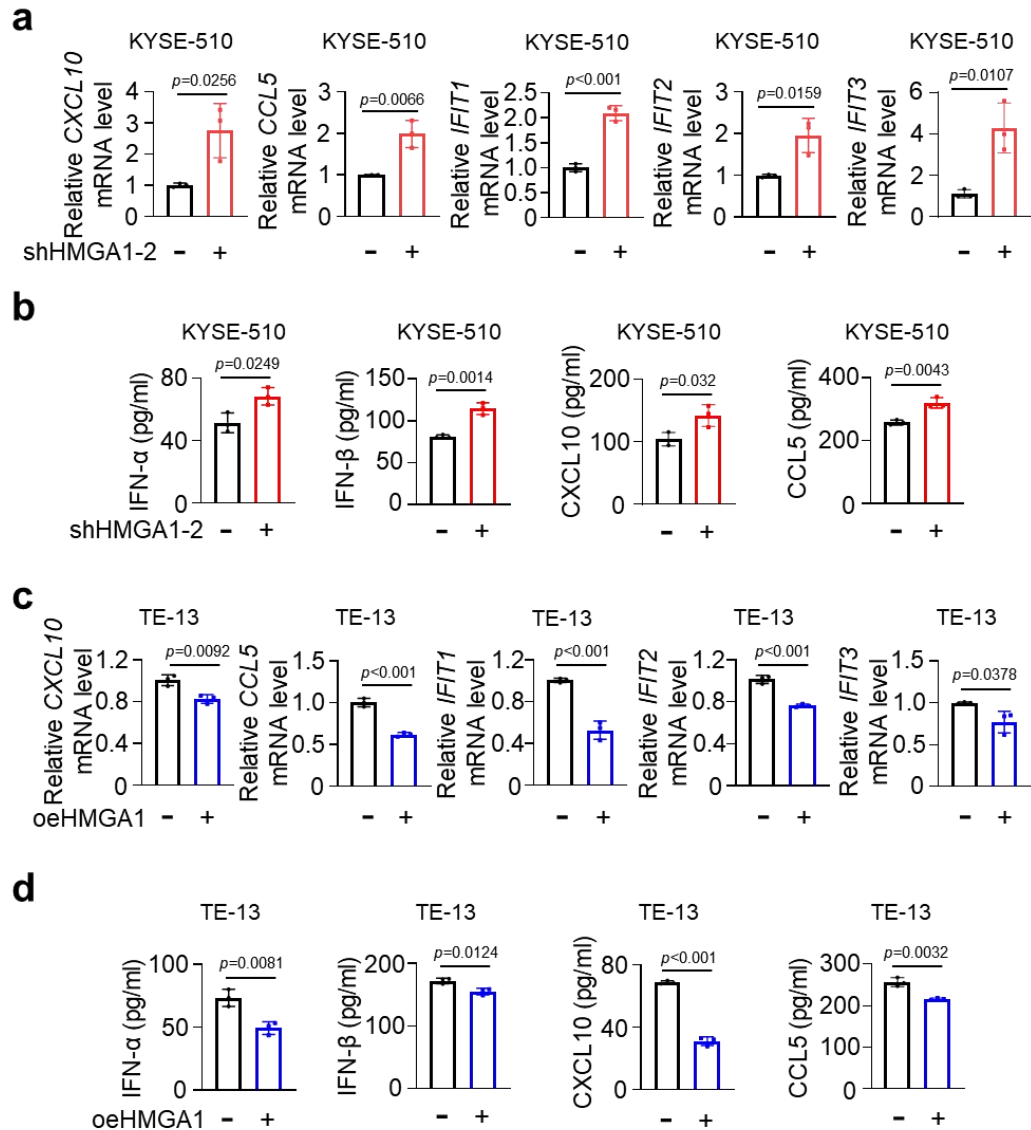


**Supplementary Fig. 1 Expression of HMGA1 in human ESCC cells and construction of HMGA1-manipulated cell lines. a** Expression of HMGA1 in different ESCC cell lines, assessed by western blot. **b** Levels of *HMGA1* in various ESCC cell lines measured by qPCR. **c-f** Knockdown efficiency of two shRNA duplexes targeting HMGA1 in KYSE-30 and KYSE-510 cells, as determined by western blot. **g** Confirmation of HMGA1 overexpression in KYSE-70 and TE-13 cells by western blot. Data are expressed as mean  $\pm$  SD. Statistical significance was

determined by two-tailed unpaired t-test (**a**, **b**, **d**, **f**). Sample sizes: (**a-g**)  $n = 3$  independent experiments. Image in **a**, **c**, **e**, **g** shows representative results from three independent experiments. Source data are provided in the Source Data file.



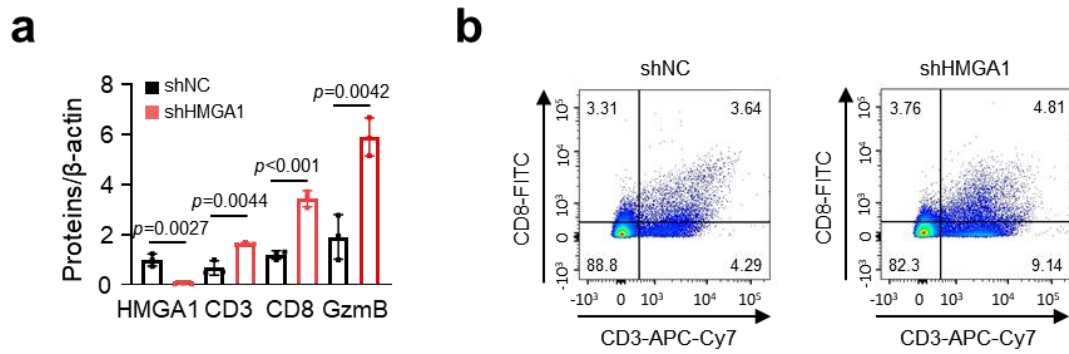
**Supplementary Fig. 2 Statistical analysis of the RNA sequencing data.** mRNA levels of *HMGA1* and inflammatory cytokines in shNC-30 and shHMGA1-30-1 cells from RNA-seq analysis ( $n = 3$ , independent experiments). RNA-seq was performed in 3 biological replicates. Statistical analysis was conducted using the DESeq2 program in R, with p-values calculated based on a negative binomial distribution. ns, no statistical difference. Data are presented as mean  $\pm$  SD. Source data are provided in the Source Data file.



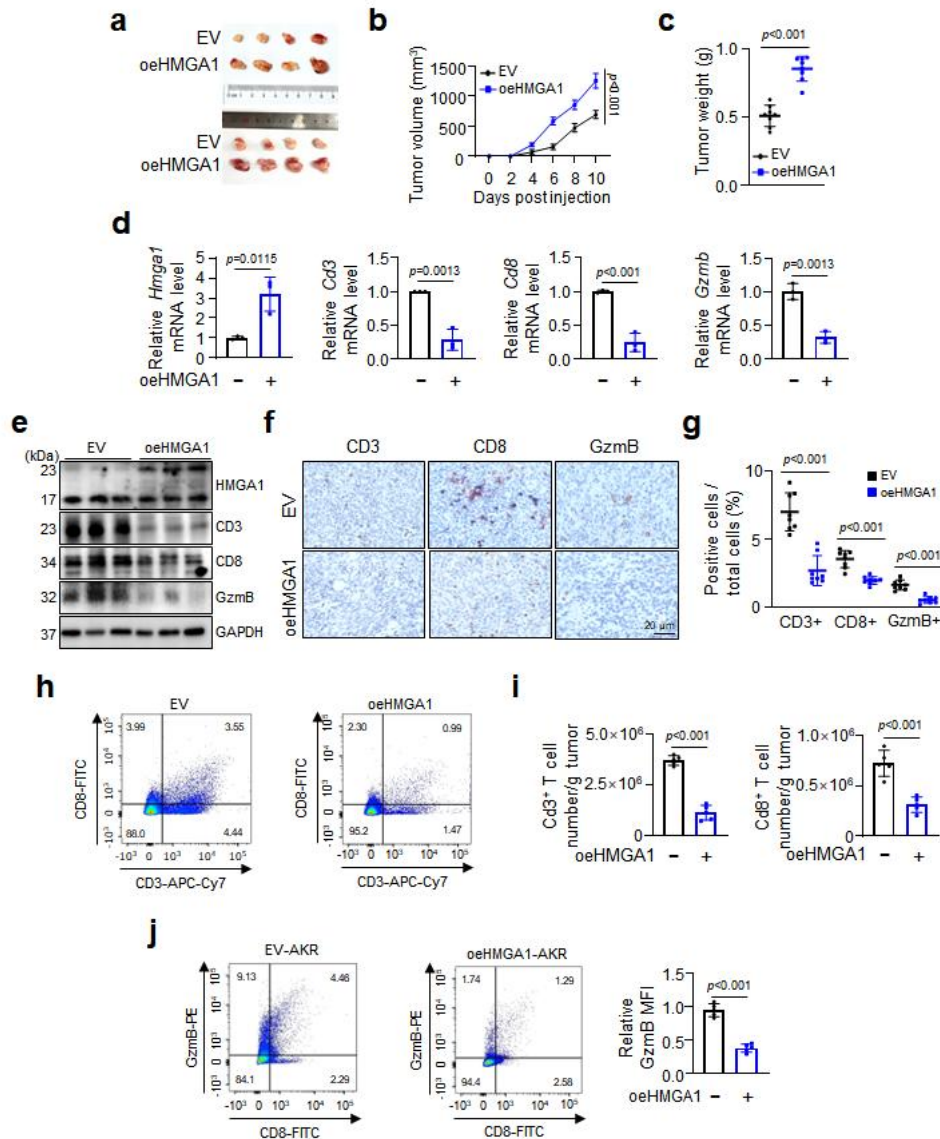
**Supplementary Fig. 3 Expression of ISGs in HMGA1-manipulated cells. a, b**

Depletion of HMGA1 increases the expression of interferon-stimulating genes (ISGs) and ISG-related inflammatory factors in ESCC cells. KYSE-510 cells were transfected with shNC or shHMGA1-2 to create stable cell lines. RNAs were extracted from these cells and analyzed by qPCR to determine the levels of ISGs and ISG-related inflammatory factors (**a**). Supernatants of the cell culture were collected and analyzed with ELISA kits to measure the levels of IFN- $\alpha$ , IFN- $\beta$ , CXCL10, and CCL5 (**b**). **c, d** Overexpression of HMGA1 reduces ISGs and ISG-related inflammatory factors in

ESCC cells. TE-13 cells were transduced with EV or oeHMGA1 constructs to create stable cell lines. RNAs were extracted from these cells and analyzed by qPCR for ISGs and ISG-related inflammatory factors (**c**). Supernatants from the cell cultures were collected and analyzed with ELISA kits to measure IFN- $\alpha$ , IFN- $\beta$ , CXCL10, and CCL5 (**d**). Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a-d**). Sample sizes: (**a-d**) n = 3 independent experiments. Source data are provided in the Source Data file.

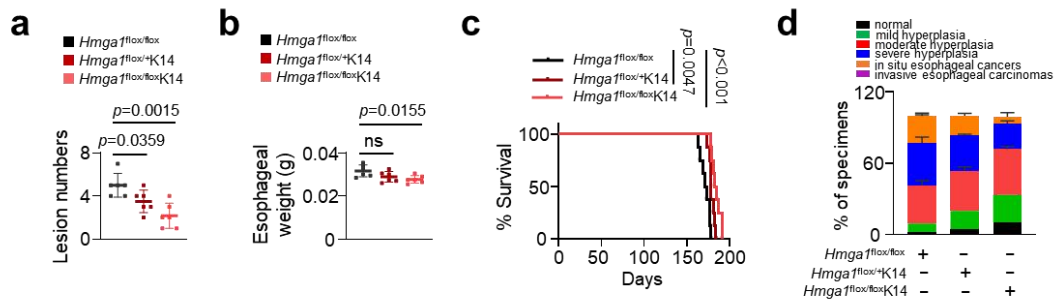


**Supplementary Fig. 4 CD3<sup>+</sup>/CD8<sup>+</sup> T cells in HMGA1-depleted subcutaneous tumors analyzed.** **a** CD3, CD8, and GzmB expression in subcutaneous tumors was assessed by western blot in Fig. 2e. **b** shNC-AKR and shHMGA1-AKR cells were transplanted into the right front flank of C57BL/6 mice. Subcutaneous allografts were dissociated and subjected to mechanical disruption and digestion with collagenase IV and DNase I. Flow cytometry was used to detect CD3<sup>+</sup>/CD8<sup>+</sup> T cells in the subcutaneous tumors. Data are expressed as mean ± SD. Statistical significance was determined by two-tailed unpaired t-test (**a**). Sample sizes: (**a**)  $n = 3$ ; (**b**)  $n = 5$  independent mice. Image in **b** shows representative results from three independent experiments. Source data are provided in the Source Data file.

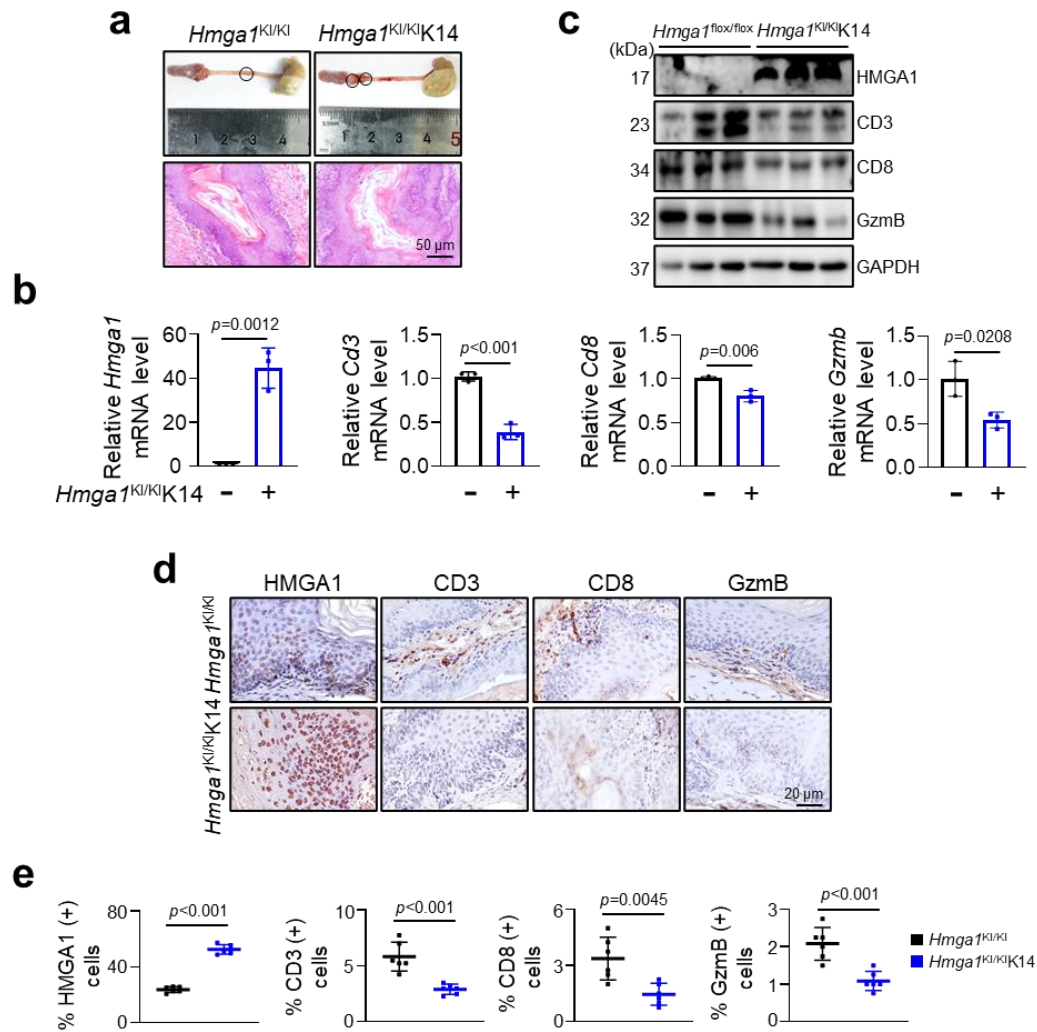


**Supplementary Fig. 5 HMGGA1 inhibits the infiltration of T cells into ESCC and promotes the growth of syngeneic ESCC allografts.** a-j C57BL/6 mice were subcutaneously inoculated with EV-AKR and oeHMGGA1-AKR cells, respectively. The mice were sacrificed on day 10 to collect subcutaneous tumors. **a** Photos of syngeneic ESCC allografts. **b** Tumor size in mice was measured every two days with calipers. **c** Tumor weight on day 10. **d** Levels of *Cd3*, *Cd8*, and *Gzmb* in tumors were measured by qPCR. **e** Expression of CD3, CD8, and GzmB in tumors by western blot analysis. The samples derive from the same experiment but different gels for HMGGA1,

CD3, CD8, GZMB and another for GAPDH were processed in parallel. GAPDH served as loading control. **f** IHC staining of CD3, CD8, and GzmB in tumors. Scale bar: 20  $\mu$ m. **g** Percentage of CD3, CD8, and GzmB positive cells from **f**. **h** Detection of CD3<sup>+</sup>/CD8<sup>+</sup> T cells in tumors by flow cytometry analysis. **i** Quantitation of CD3<sup>+</sup>/CD8<sup>+</sup> T cells in tumors by flow cytometry. **j** Expression of GzmB in CD8<sup>+</sup> T cells in tumors, with the mean fluorescence intensity (MFI) presented in the right panel. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b**, **c**, **d**, **g**, **i**, **j**). Sample sizes: (**a**, **b**, **c**, **f**, **g**)  $n = 8$ ; (**d**, **e**)  $n = 3$ ; (**h-j**)  $n = 5$  independent mice. Image in **e**, **f**, **h**, **j** shows representative results from three independent experiments. Source data are provided in the Source Data file.

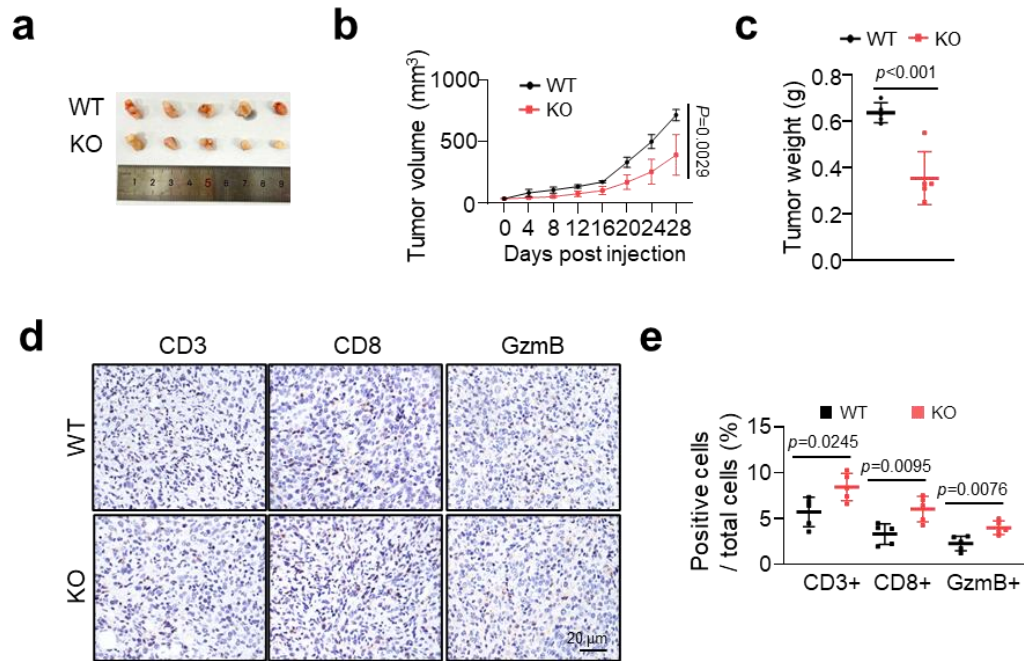


**Supplementary Fig. 6 HMGA1 conditional knockout in the esophagus promotes ESCC tumorigenesis.** **a-d** HMGA1 conditional knockout in the esophagus ( $Hmga1^{flox/floxK14}$ ), HMGA1<sup>+/-</sup> ( $Hmga1^{flox/+K14}$ ), and control ( $Hmga1^{flox/flox}$ ) mice were treated with 80 mg/L 4NQO in drinking water to induce ESCC. **a** Number of esophageal lesions in mice. **b** Esophageal weight of mice. **c** Survival rate of mice. **d** Percentage of pathological alterations in esophageal tissues from the mice. ns, no statistical difference. Data are presented as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**, **b**) or Gehan-Breslow-Wilcoxon test (**c**). Sample sizes: (**a**, **b**, **d**)  $n = 6$ ; (**c**)  $n = 8$  independent mice. Source data are provided as a Source Data file.



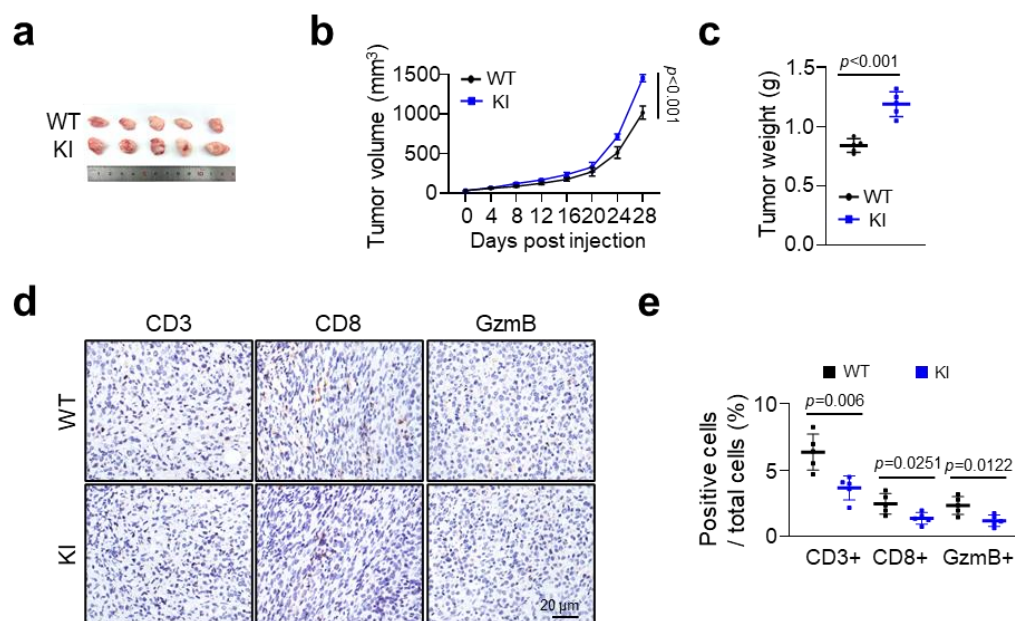
**Supplementary Fig. 7 HMGA1 conditional knock-in in the esophagus suppresses the infiltration of T lymphocytes and promotes tumorigenesis of ESCC.** **a-e** *Hmga1*<sup>KI/KI</sup> (control) and *Hmga1*<sup>KI/KI</sup>K14 (HMGA1 conditional knock-in) mice were treated with 80 mg/L 4NQO in drinking water for 5 months to induce ESCC. At the end of the induction, mice were sacrificed and the esophagus was isolated. **a** Representative images of 4NQO-induced ESCC in the mice. Upper panel: macroscopic view of the esophagus, with circles indicating tumor locations. Bottom panel: representative HE staining of esophageal tissues. **b** Levels of *Cd3*, *Cd8*, and *Gzmb* in ESCCs of the mice by qPCR analysis. RNAs were extracted from

4NQO-induced ESCCs in the mice and analyzed by qPCR. **c** Expression of CD3, CD8, and GzmB in ESCCs in the mice by western blot analysis. The samples derive from the same experiment but different gels for HMGA1, CD3, CD8, GZMB and another for GAPDH were processed in parallel. GAPDH served as loading control. **d** IHC staining of CD3, CD8, and GzmB in 4NQO-induced mouse ESCCs and adjacent esophagus. Scale bar: 20  $\mu$ m. **e** Percentage of CD3, CD8, and GzmB positive cells from IHC staining in **d**. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b**, **e**). Sample sizes: (**a**, **d**, **e**)  $n = 6$ ; (**b**, **c**)  $n = 3$  independent mice. Image in **a**, **c**, **d** shows representative results from three independent experiments. Source data are provided in the Source Data file.

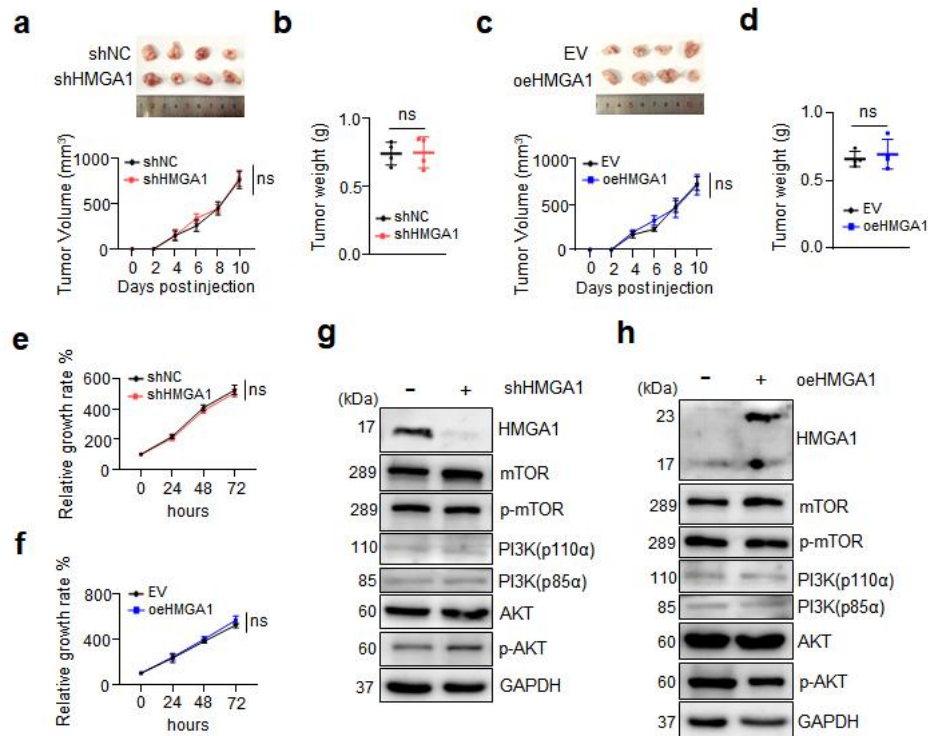


**Supplementary Fig. 8 Knockout of HMGA1 promotes the infiltration of T cells in allografts from syngeneic mouse ESCC.** *Hmga1*<sup>flox/flox</sup> (WT) and *Hmga1*<sup>flox/flox</sup>K14 (KO) mice were exposed to 80 mg/L 4NQO in drinking water for 5 months to induce ESCC. At the end of the induction, mice were sacrificed, and esophageal tumors were resected. Tumor pieces (2-5 mm) were implanted subcutaneously into the right front flank of C57BL/6 mice. When the successfully established syngeneic mouse allografts reached ~500 mm<sup>3</sup>, the tumors were transplanted to other mice. Mice bearing third passage grafts were used to examine the effect of HMGA1 on tumor growth. Tumor volumes were measured every 4 days. **a** Representative images of third passage tumors on day 28. **b** Tumor size in mice measured every 4 days with calipers. **c** Tumor weight. **d, e** Expression and quantitation of CD3, CD8, and GzmB in tumors by IHC staining. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b, c, e**). Sample sizes: (**a-e**)  $n = 5$  independent mice. Image in **d** shows representative results from three independent

experiments. Source data are provided in the Source Data file.

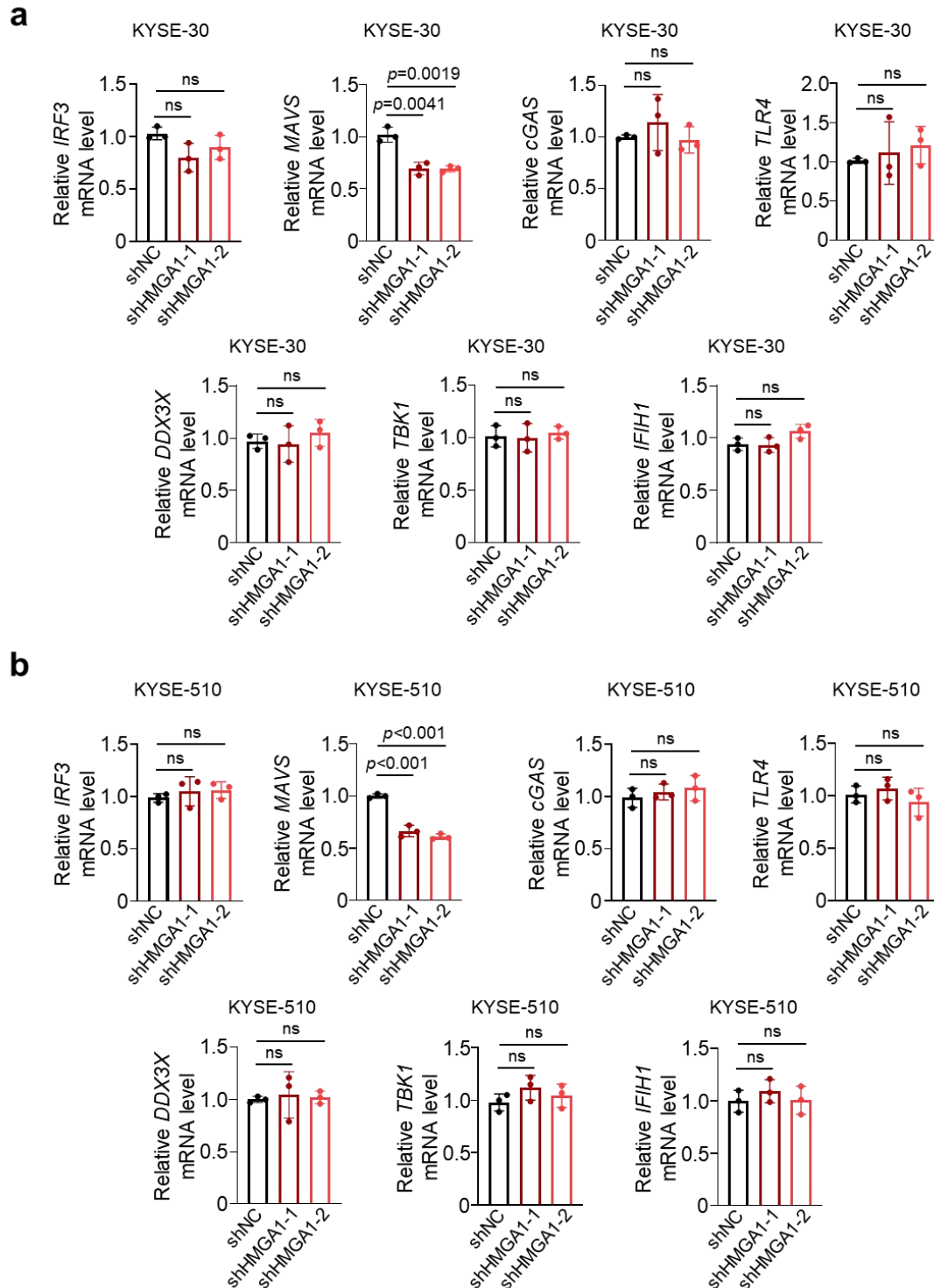


**Supplementary Fig. 9 Knock-in of HMGA1 inhibits the infiltration of T cells in allografts from syngeneic mouse ESCC.** *Hmga1*<sup>KI/KI</sup> (WT) and *Hmga1*<sup>KI/KI</sup>K14 (KI) mice were exposed to 80 mg/L 4NQO in drinking water for 5 months to induce ESCC. At the end of the induction, mice were sacrificed, and esophageal tumors were resected. Allografts from primary ESCC of the mice were established in syngeneic C57BL/6 mice as described in Supplementary Fig. 8. **a** Representative images of third passage tumors on day 28. **b** Tumor size in mice measured every 4 days with calipers. **c** Tumor weight. **d, e** Expression and quantitation of CD3, CD8, and GzmB in tumors by IHC staining. Scale bar: 20 μm. Data are expressed as mean ± SD. Statistical significance was determined by two-tailed unpaired t-test (**b, c, e**). Sample sizes: (**a-e**) n = 5 independent mice. Image in **d** shows representative results from three independent experiments. Source data are provided in the Source Data file.



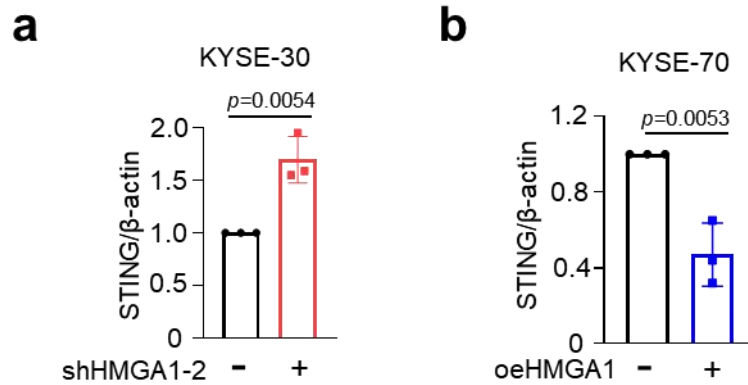
**Supplementary Fig. 10 HMGA1 does not affect ESCC cell growth *in vitro* and in nude mice.** **a, b** Nude mice were subcutaneously inoculated with shNC-AKR or shHMGA1-AKR cells. Tumor size in the mice was measured every other day with calipers (bottom panel). Mice were sacrificed on day 10, and the xenografts were removed (upper panel). Tumors weight on day 10 are shown (**b**). **c, d** Nude mice were subcutaneously inoculated with EV-AKR or oeHMGA1-AKR cells. Tumor size in the mice was measured every other day with calipers (bottom panel). Mice were sacrificed on day 10, and the xenografts were removed (upper panel). Tumor weight on day 10 are shown (**d**). **e, f** Cell proliferation of shNC-AKR and shHMGA1-AKR cells (**e**), and EV-AKR and oeHMGA1-AKR cells (**f**) was determined by CCK8 assay. **g, h** Western blot was used to detect the expression of PI3K (p100 $\alpha$ ), PI3K (p85 $\alpha$ ), AKT, p-AKT, mTOR, and p-mTOR in HMGA1-manipulated cells. The samples derive from the same experiment but different gels for HMGA1, PI3K (p100 $\alpha$ ), PI3K (p85 $\alpha$ ), AKT,

p-AKT, mTOR, p-mTOR and another for GAPDH were processed in parallel. GAPDH served as loading control. ns, no statistical difference. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a-f**). Sample sizes: (**a-d**) n = 4 independent mice; (**e, f**) n = 4; (**g, h**) n = 3 independent experiments. Image in **g, h** shows representative results from three independent experiments. Source data are provided in the Source Data file.



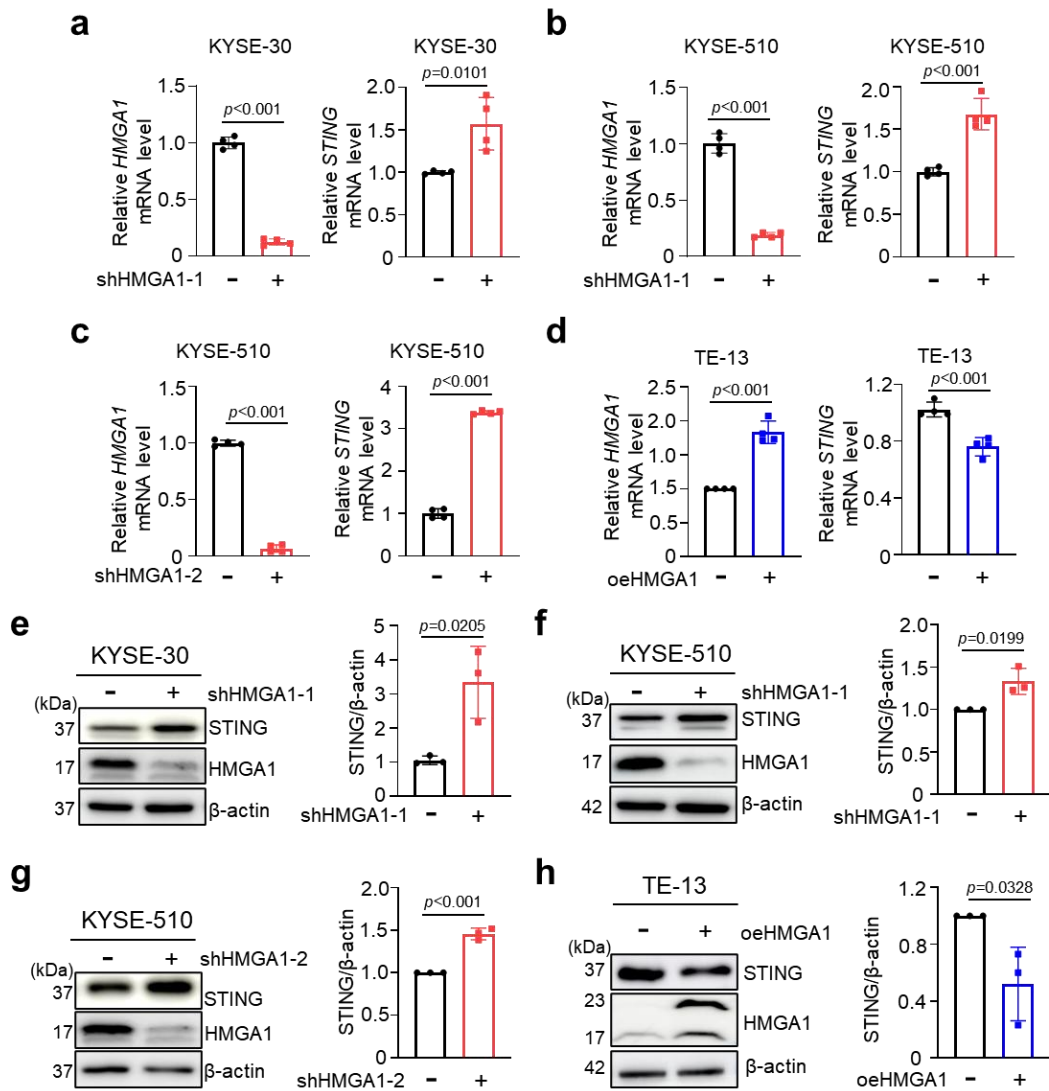
**Supplementary Fig. 11 Expression of immune-related genes.** **a** RNAs were extracted from KYSE-30 cells transfected with shNC, shHMGA1-1, and shHMGA1-2. After reverse transcription, qPCR was performed to detect the expression of immune-related genes. **b** RNAs were extracted from KYSE-510 cells transfected with

shNC, shHMGA1-1, and shHMGA1-2. After reverse transcription, qPCR was performed to detect the expression of immune-related genes. ns, no statistical difference. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**, **b**). Sample sizes: (**a**, **b**) n = 3 independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 12 Quantitation of STING in HMGA1-manipulated cells.**

STING levels in HMGA1 knockdown (**a**) and overexpression (**b**) cells were detected in Fig.3e and 3f by western blot. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**, **b**). Sample sizes: (**a**, **b**)  $n = 3$  independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 13 HMGA1 negatively regulates STING expression. a-d**

Levels of *STING* in HMGA1-manipulated cells were determined by qPCR.

Proliferating shNC-30 and shHMGA1-30-1 cells (**a**), shNC-510 and shHMGA1-510-1

cells (**b**), shNC-510 and shHMGA1-510-2 cells (**c**), and EV-TE-13 and

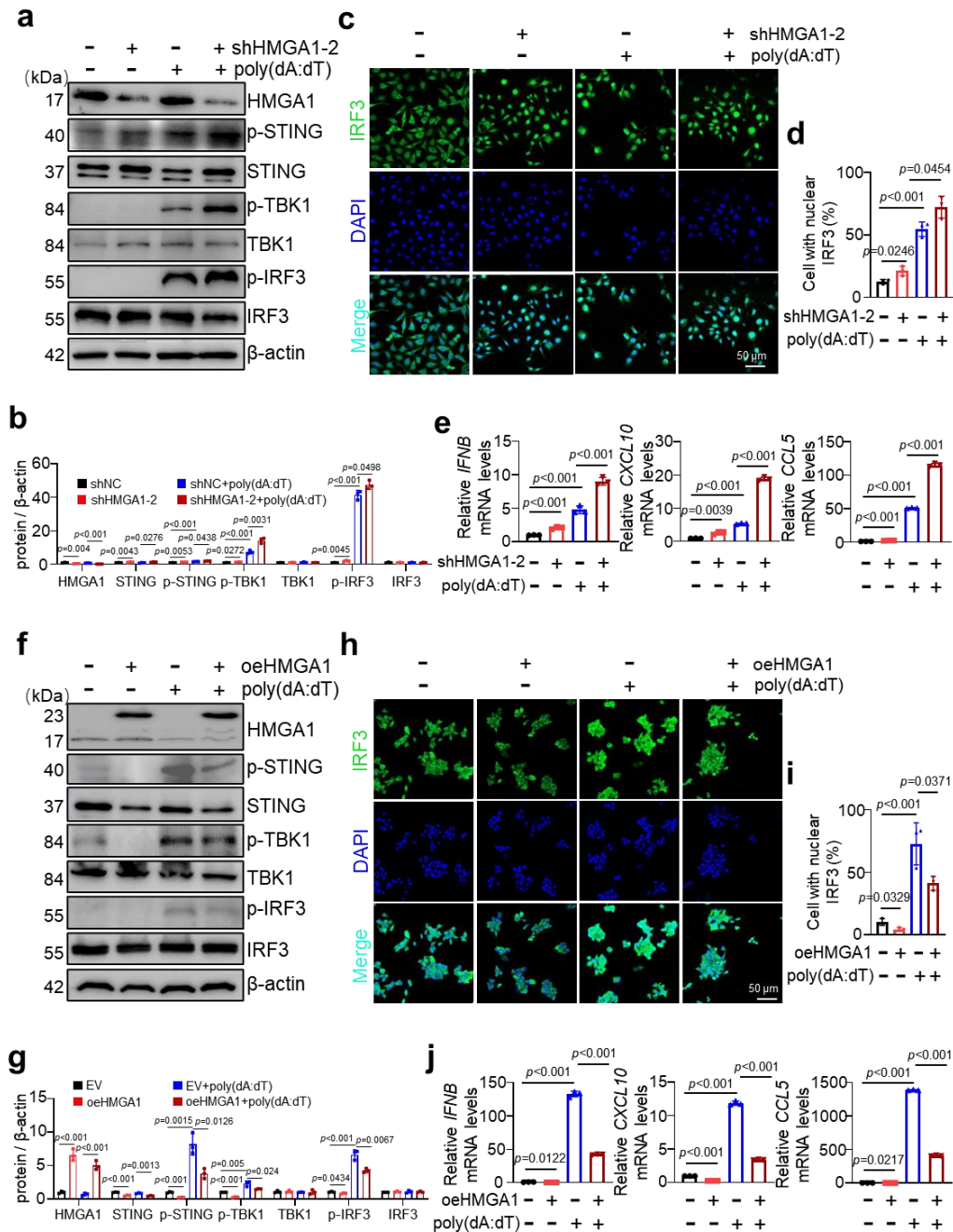
oeHMGA1-TE-13 cells (**d**) were collected for RNA extraction. After reverse

transcription, qPCR was used to amplify *STING*. **e-h** Expression of STING in

HMGA1-manipulated cells was determined by western blot. Proliferating shNC-30

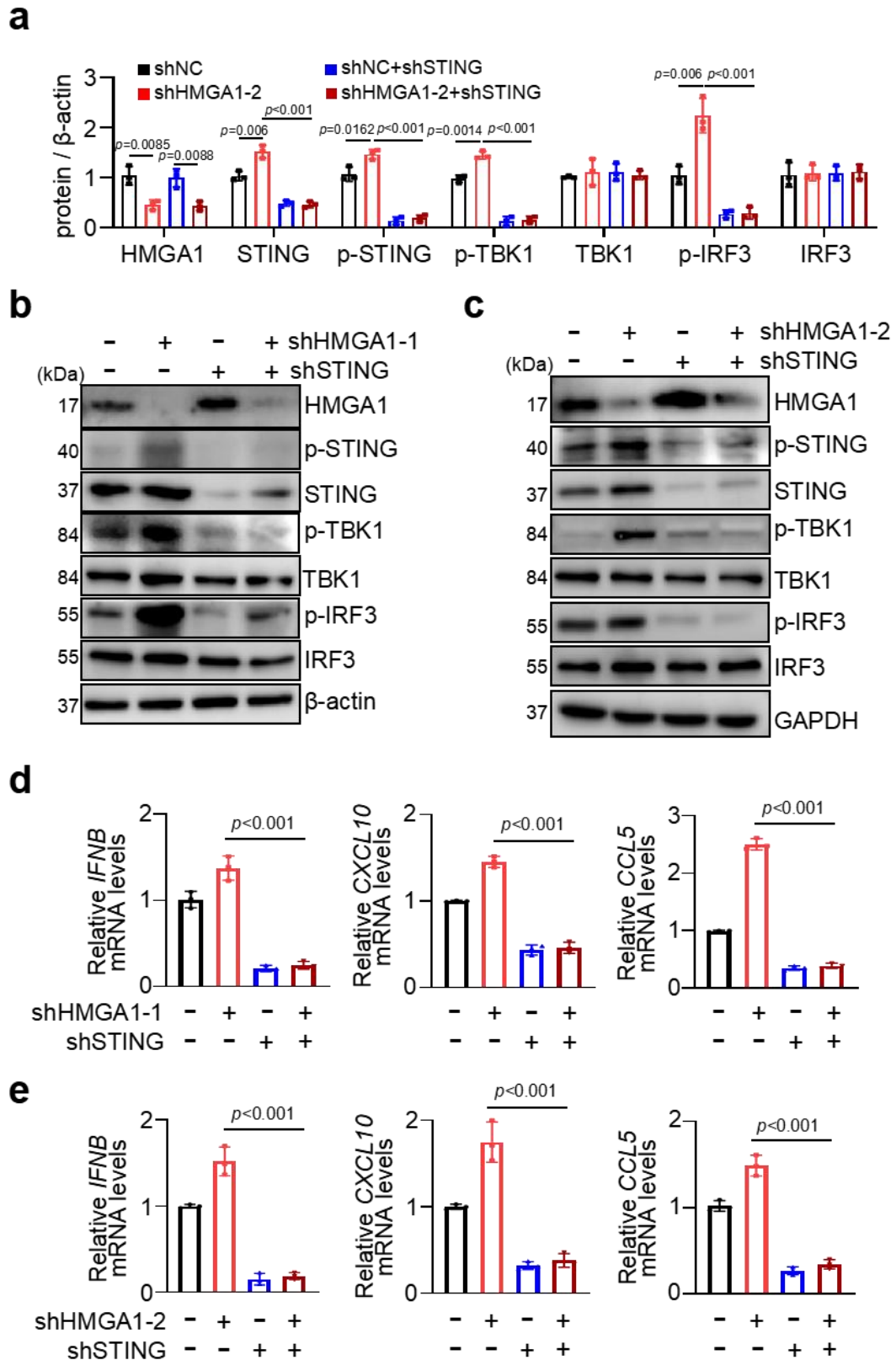
and shHMGA1-30-1 cells (**e**), shNC-510 and shHMGA1-510-1 cells (**f**), shNC-510 and

shHMGA1-510-2 cells (**g**), and EV-TE-13 and oeHMGA1-TE-13 cells (**h**) were collected for whole cell extracts. Western blot was used to detect STING expression. Quantitation of STING expression was performed using ImageJ. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a-h**). Sample sizes: (**a-d**) n = 4; (**e-h**) n = 3 independent experiments. Image in **e-h** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 14 Inhibition of HMGA1 promotes dsDNA-stimulated STING signaling.** **a, b** HMGA1-knockdown KYSE-30 cells were treated with 1  $\mu$ g/mL poly(dA:dT) for 24 hours. Expression of STING and its downstream targets was detected by western blot. The samples derive from the same experiment but different gels for HMGA1, STING, p-STING, p-TBK1, TBK1, p-IRF3, IRF3, and another for  $\beta$ -actin were processed in parallel.  $\beta$ -actin served as loading control. **c, d** Distribution

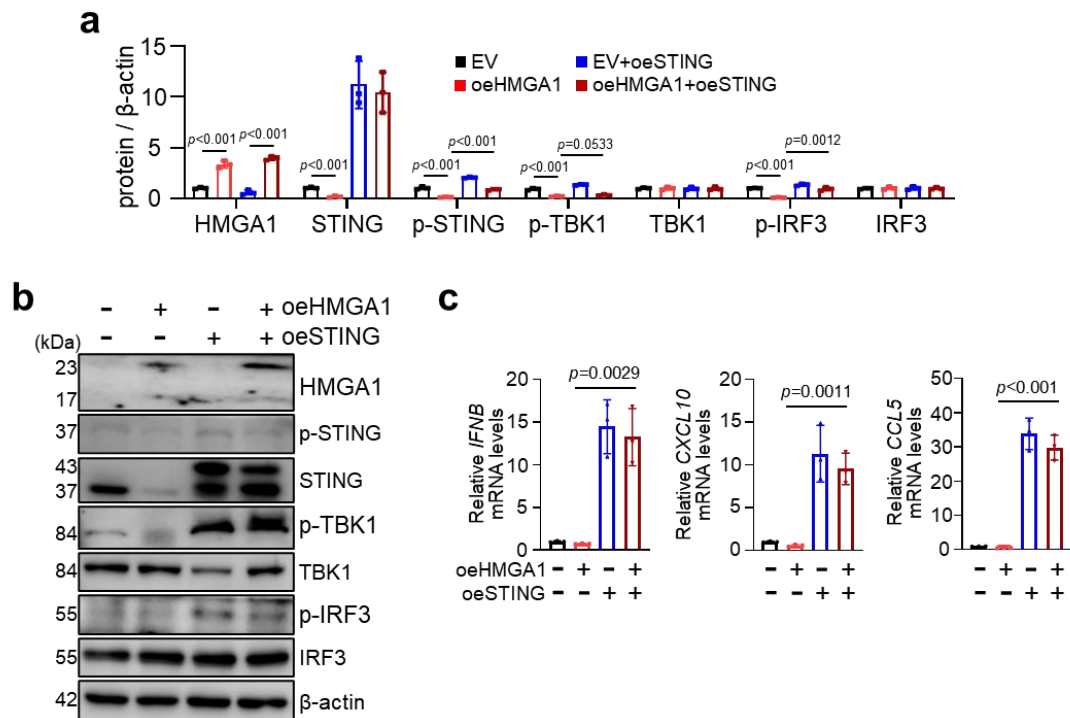
of IRF3 in the nucleus (Nuc) and cytoplasm (Cyt) was detected by immunofluorescence in shNC-30 and shHMGA1-30-2 cells treated with poly(dA:dT) for 12 hours. Scale bar: 50  $\mu$ m. **e** qPCR was used to detect the expression of *IFNB*, *CXCL10*, and *CCL5* in KYSE-30 cells transfected with shHMGA1-2 and stimulated with 1  $\mu$ g/mL poly(dA:dT) for 24 hours. **f, g** HMGA1-overexpressing KYSE-70 cells were treated with 1  $\mu$ g/mL poly(dA:dT) for 24 hours. Expression of STING downstream targets was detected by western blot. The samples derive from the same experiment but different gels for HMGA1, STING, p-STING, p-TBK1, TBK1, p-IRF3, IRF3, and another for  $\beta$ -actin were processed in parallel.  $\beta$ -actin served as loading control. **h, i** The expression of IRF3 in the nucleus (Nuc) and cytoplasm (Cyt) was determined by immunofluorescence in EV-70 and oeHMGA1-70 cells transfected with poly(dA:dT) for 12 hours. Scale bar: 50  $\mu$ m. **j** qPCR was used to detect the expression of *IFNB*, *CXCL10*, and *CCL5* in KYSE-70 cells transfected with oeHMGA1 and stimulated with 1  $\mu$ g/mL poly(dA:dT) for 24 hours. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b, d, e, g, i, j**). Sample sizes: (**a-j**) n=3 independent experiments. Image in **a, c, f, h** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 15 STING mediates upregulation of inflammatory cytokines**

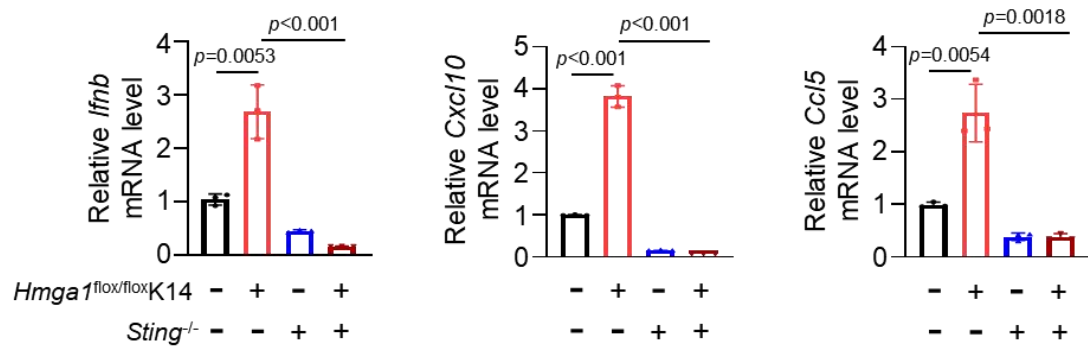
**induced by HMGGA1 depletion in ESCC cells. a** STING and its downstream targets

in HMGA1 knockdown and/or STING knockdown cells were detected in Fig. 4a by western blot. Expression of these targets in the cells was quantified using data from 3 independent experiments. **b, c** Western blot analysis of p-STING, p-TBK1, and p-IRF3 in shNC-510 and shHMGA1-510-1 cells (**b**), and shNC-510 and shHMGA1-510-2 cells (**c**) co-transfected with shSTING. The samples derive from the same experiment but different gels for HMGA1, STING, p-STING, p-TBK1, TBK1, p-IRF3, IRF3, and another for  $\beta$ -actin or GAPDH were processed in parallel.  $\beta$ -actin or GAPDH served as loading control. **d, e** qPCR analysis of *IFNB*, *CXCL10*, and *CCL5* in shNC-510 and shHMGA1-510-1 cells (**d**), and shNC-510 and shHMGA1-510-2 cells (**e**) co-transfected with shSTING. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a, d, e**). Sample sizes: (**a-e**)  $n = 3$  independent experiments. Image in **b, c** shows representative results from three independent experiments. Source data are provided in the Source Data file.

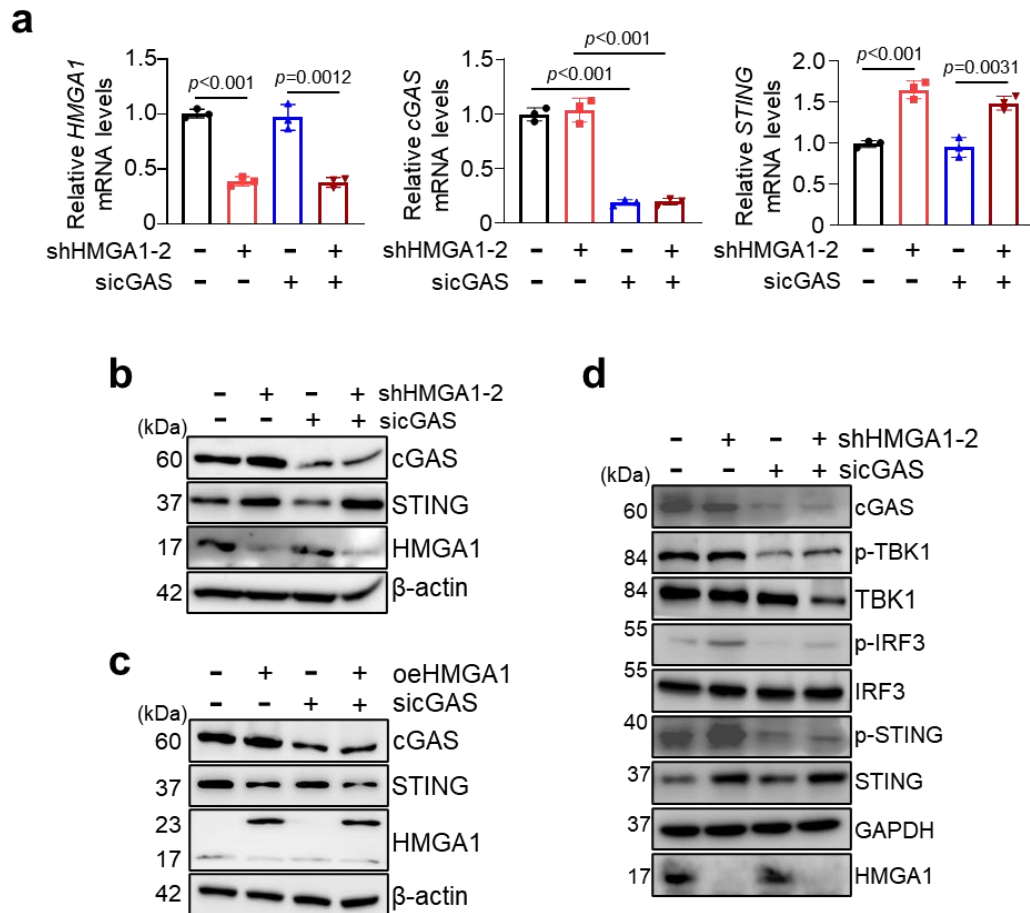


**Supplementary Fig. 16 Overexpression of STING reverses HMGA1-induced downregulation of inflammatory cytokines in ESCC cells.** **a** STING and its downstream targets in HMGA1 and/or STING overexpression cells were detected in Fig. 4c by western blot. Expression of these targets in the cells was quantified using data from 3 independent experiments. **b** Western blot analysis of p-STING, p-TBK1, and p-IRF3 in EV-TE-13 and oeHMGA1-TE-13 cells co-transfected with oeSTING. The samples derive from the same experiment but different gels for HMGA1, STING, p-STING, p-TBK1, TBK1, p-IRF3, IRF3, and another for  $\beta$ -actin were processed in parallel.  $\beta$ -actin served as loading control. **c** qPCR analysis of *IFNB*, *CXCL10*, and *CCL5* in EV-TE-13 and oeHMGA1-TE-13 cells co-transfected with oeSTING. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**, **c**). Sample sizes: (**a-c**)  $n = 3$  independent experiments. Image in **b** shows representative results from three independent experiments. Source data are

provided in the Source Data file.

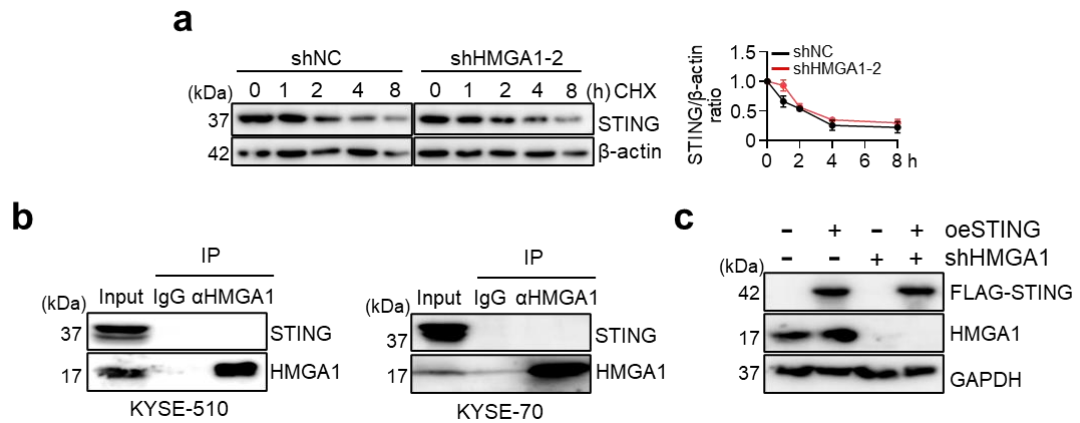


**Supplementary Fig. 17 STING mediates upregulation of inflammatory cytokines in HMGA1 depleted mouse ESCC.** *Hmga1*<sup>flox/flox</sup>, *Hmga1*<sup>flox/flox</sup>K14, *Sting*<sup>-/-</sup>, and *Hmga1*<sup>flox/flox</sup>K14*Sting*<sup>-/-</sup> mice were exposed to 4NQO in drinking water for 5 months for the induction of ESCC. At the end of the experiment, murine ESCCs or esophageal epithelia were collected for mRNA isolation. qPCR was used to detect the expression of *Ifnb*, *Cxcl10*, and *Ccl5* in ESCCs (esophageal tissues) from the mice (n = 3, independent experiments). Data are expressed as mean ± SD. Statistical significance was determined by two-tailed unpaired t-test. Source data are provided in the Source Data file.



**Supplementary Fig. 18 HMGA1 inhibits STING independently of cGAS.** **a** qPCR analysis of STING in shNC-30 and shHMGA1-30-2 cells transfected with cGAS siRNA. **b** Western blot analysis of STING in shNC-510 and shHMGA1-510-2 cells transfected with cGAS siRNA. The samples derive from the same experiment but different gels for HMGA1, STING, cGAS, and another for  $\beta$ -actin were processed in parallel.  $\beta$ -actin served as loading control. **c** Western blot analysis of STING in EV-70 and oeHMGA1-70 cells transfected with cGAS siRNA. The samples derive from the same experiment but different gels for HMGA1, STING, cGAS, and another for  $\beta$ -actin were processed in parallel.  $\beta$ -actin served as loading control. **d** Western blot analysis of p-STING, p-TBK1, and p-IRF3 in shNC-30 and shHMGA1-30-2 cells transfected with cGAS siRNA. The samples derive from the same experiment but different gels for

HMGA1, STING, p-STING, p-TBK1, TBK1, p-IRF3, IRF3, and another for GAPDH were processed in parallel. GAPDH served as loading control. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**). Sample sizes: (**a-d**) n = 3 independent experiments. Image in **b-d** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 19 HMGA1 does not regulate STING stability at the protein**

**level or interact directly with STING.** **a** Western blot was used to detect the

expression of STING (half-life) in KYSE-510 cells transduced with shHMGA1-2 and

treated with CHX (100  $\mu$ g/mL) for 0 h, 1 h, 2 h, 4 h, and 8 h. **b** Co-immunoprecipitation

assay detecting the interaction between HMGA1 and STING in KYSE-510 and

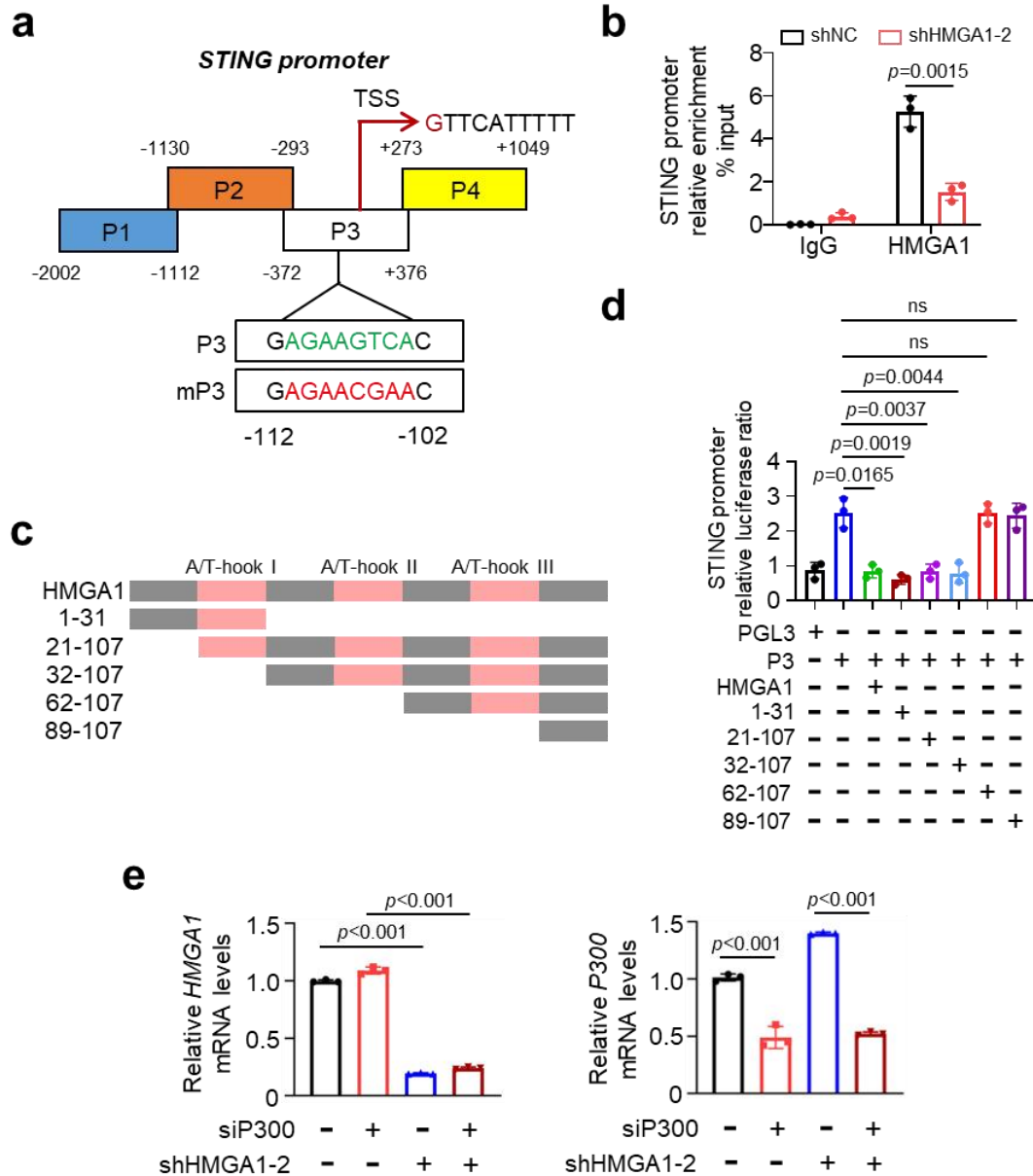
KYSE-70 cells. **c** EV-510 and oeSTING-510 were transduced with shNC and

shHMGA1. The expression of HMGA1 and exogenous STING (tagged with FLAG)

was detected by Western blot. Data are expressed as mean  $\pm$  SD. Sample sizes: **(a-c)**

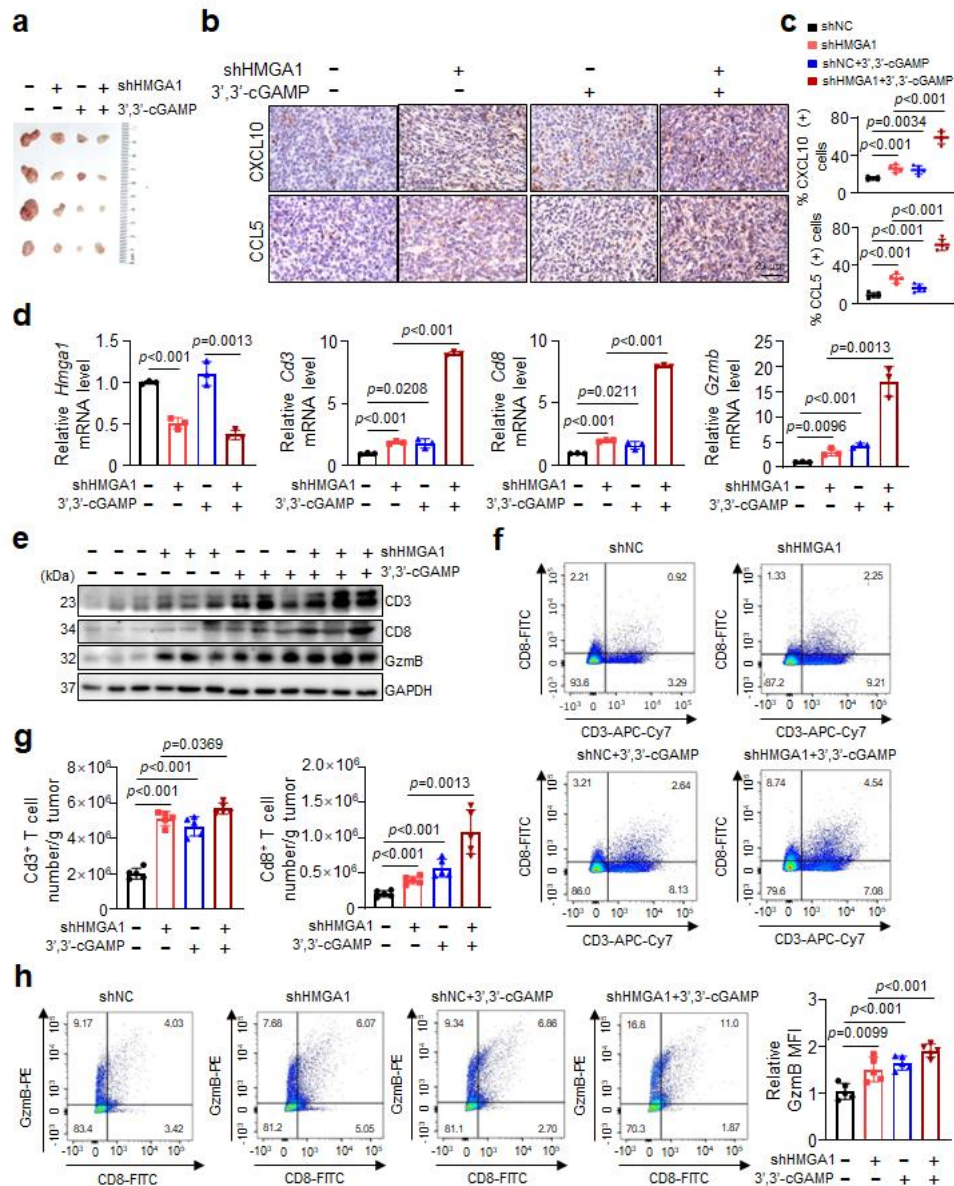
n = 3 independent experiments. Image in **a-c** shows representative results from three

independent experiments. Source data are provided in the Source Data file.



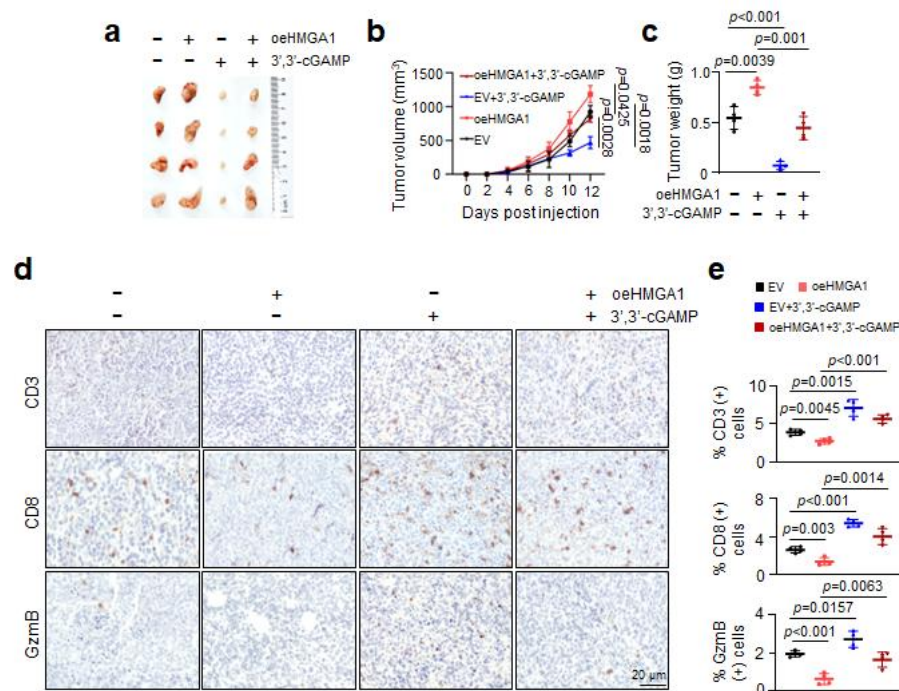
**Supplementary Fig. 20 HMGA1 inhibits the transcription of STING.** **a** Schematic diagram of human STING promoter fragments used for segmented amplification (P1: -2002bp/-1112bp; P2: -1130bp/-293bp; P3: -372bp/+376bp; P4: +273bp/+1049bp). The CREB binding site in the P3 fragment and its mutation are highlighted. **b** ChIP-qPCR assay detecting HMGA1 binding to the STING promoter. Anti-HMGA1 antibody was used to pull down chromatin in shNC-30 and shHMGA1-30-2 cells. The human STING promoter was amplified with qPCR as described in the Materials and

Methods. **c** Schematic diagram of the segmented structure of human HMGA1 coding sequence (CDS). **d** pGL3-STING promoter P3 was co-transduced with HMGA1 or its mutants into KYSE-30 cells. Luciferase activities were measured after 48 h. **e** *p300* and *HMGA1* mRNA levels in shNC-30 and shHMGA1-30 cells transfected with siNC or sip300 were monitored by qPCR. ns, no statistical difference. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b**, **d**, **e**). Sample sizes: (**b**, **d**, **e**)  $n = 3$  independent experiments. Source data are provided in the Source Data file.

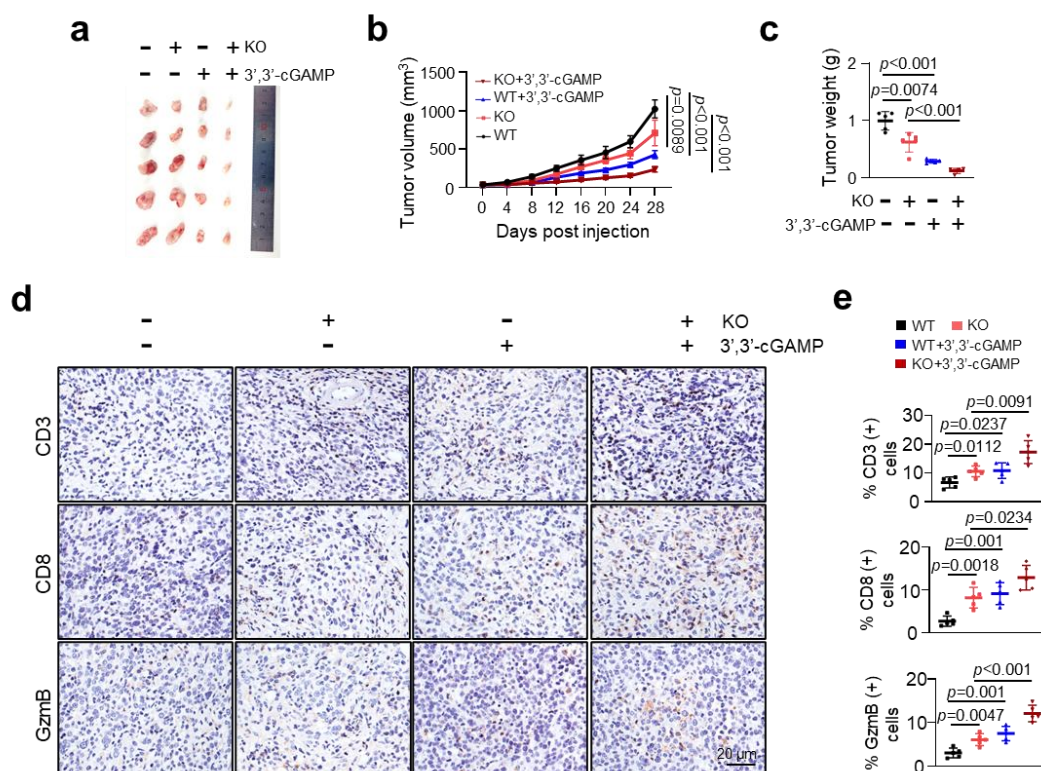


**Supplementary Fig. 21 Inhibition of HMGA1 promotes the anti-tumor effect of STING agonist 3'3'-cGAMP.** C57BL/6 mice were subcutaneously injected with  $5 \times 10^6$  shNC-AKR or shHMGA1-AKR cells in the right front flank. Three days after transplantation, mice were given 10  $\mu$ g of 3'3'-cGAMP and 3  $\mu$ L of Lipofectamine 2000 in 100  $\mu$ L PBS by intratumor injection once every 3 days. Mice were sacrificed on day 12 after transplantation, and tumors were collected for analysis. **a** Representative images of subcutaneous tumors. **b, c** Representative IHC images and quantitation of

CXCL10 and CCL5 in tumors. Scale bar: 20  $\mu$ m. **d** RNAs were extracted from subcutaneous tumors. After reverse transcription, qPCR was performed to determine the levels of *Hmga1*, *Cd3*, *Cd8*, and *Gzmb*. **e** Expression of CD3, CD8, and GzmB in tumors by western blot analysis. The samples derive from the same experiment but different gels for CD3, CD8, GZMB and another for GAPDH were processed in parallel. GAPDH served as loading control. **f** Contents of CD3<sup>+</sup>/CD8<sup>+</sup> T cells in tumors determined by flow cytometry. **g** Number of CD3<sup>+</sup> and CD8<sup>+</sup> T cells in tumors (per gram) analyzed by flow cytometry. **h** Expression of GzmB in CD8<sup>+</sup> T cells measured by flow cytometry and quantified. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**c**, **d**, **g**, **h**). Sample sizes: (**b**, **c**, **f**, **g**, **h**) n = 5; (**d**, **e**) n = 3 independent mice. Image in **b**, **e**, **f**, **h** shows representative results from three independent experiments. Source data are provided in the Source Data file.



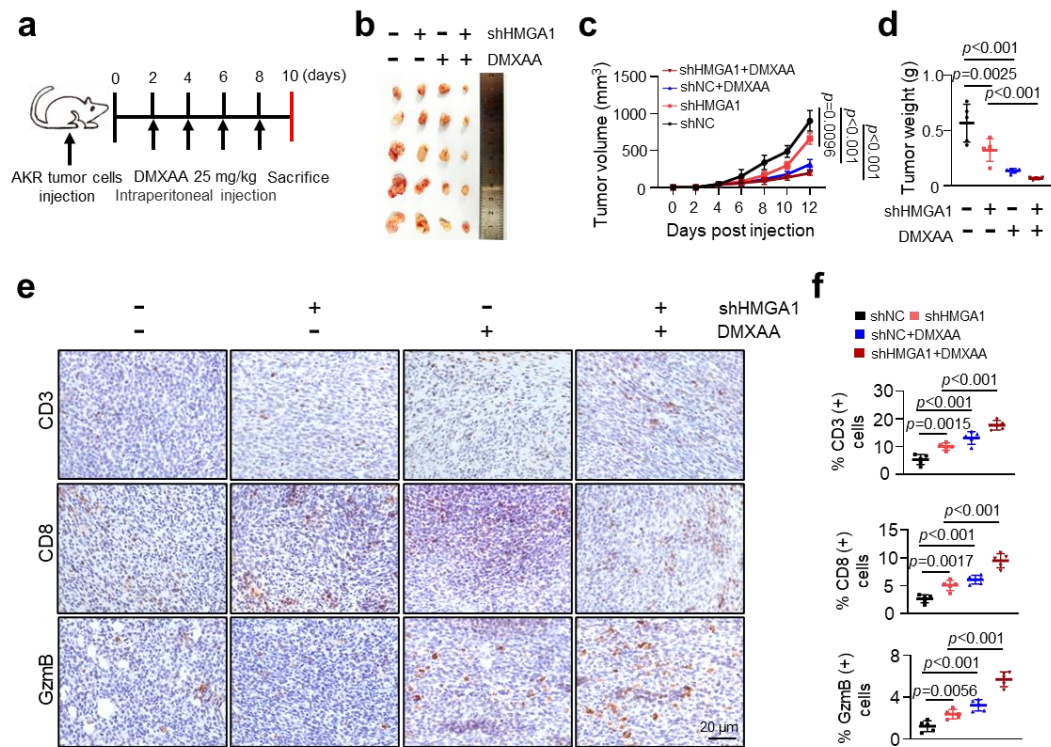
**Supplementary Fig. 22 Enforced expression of HMGA1 inhibits the anti-tumor effect of STING agonist 3'3'-cGAMP in a subcutaneous tumor model.** Murine ESCC AKR cells with or without oeHMGA1 were subcutaneously transplanted into C57BL/6 mice. 3'3'-cGAMP (10 μg each time) was administered by intratumoral injection on day 4 and day 7 as described in Fig. 6. **a** Tumors. **b** Volume of tumors. **c** Tumor weight at the time of sacrifice. **d**, **e** Representative IHC images and quantitation of CD3, CD8, and GzmB in tumors. Scale bar: 20 μm. Data are expressed as mean ± SD. Statistical significance was determined by two-tailed unpaired t-test (**b**, **c**, **e**). Sample sizes: (**a-e**) n=4 independent mice. Image in **d** shows representative results from three independent experiments. Source data are provided in the Source Data file.



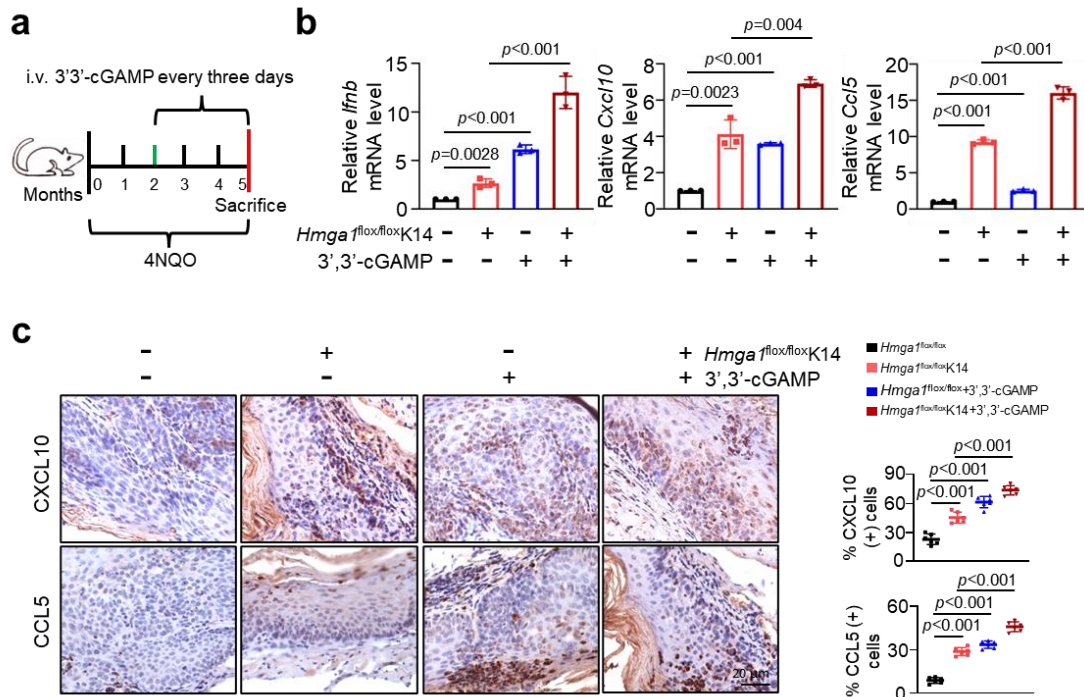
**Supplementary Fig. 23 Depletion of HMGA1 promotes the anti-tumor effect of STING agonists in syngeneic mouse allografts from murine primary ESCCs.**

*Hmga1*<sup>flx/flx</sup> and *Hmga1*<sup>flx/flx</sup>K14 mice were treated with 80 mg/L 4NQO in drinking water for 5 months to induce ESCC. At the end of induction, mice were sacrificed, and the esophagus was removed. Esophageal cancers were sliced (2 - 5 mm) and one tumor piece was implanted per mouse subcutaneously into the right flank of C57BL6 mice. When the successfully established syngeneic mouse allografts reached ~500 mm<sup>3</sup>, the tumors were transplanted to other mice. Mice bearing third passage grafts were used to examine the therapeutic effects of 3',3'-cGAMP. 3',3'-cGAMP was administered into the mice by intratumoral injection every 3 days (10 µg per mouse). Mice were sacrificed on day 28, and allografts were collected for analysis. **a** Tumors on day 28. **b** Size of tumors in mice measured every 4 days with calipers. **c** Tumor

weight. **d, e** Representative IHC images and quantitation of CD3, CD8, and GzmB in tumors. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b, c, e**). Sample sizes: (**a-e**) n = 5 independent mice. Image in **d** shows representative results from three independent experiments. Source data are provided in the Source Data file.

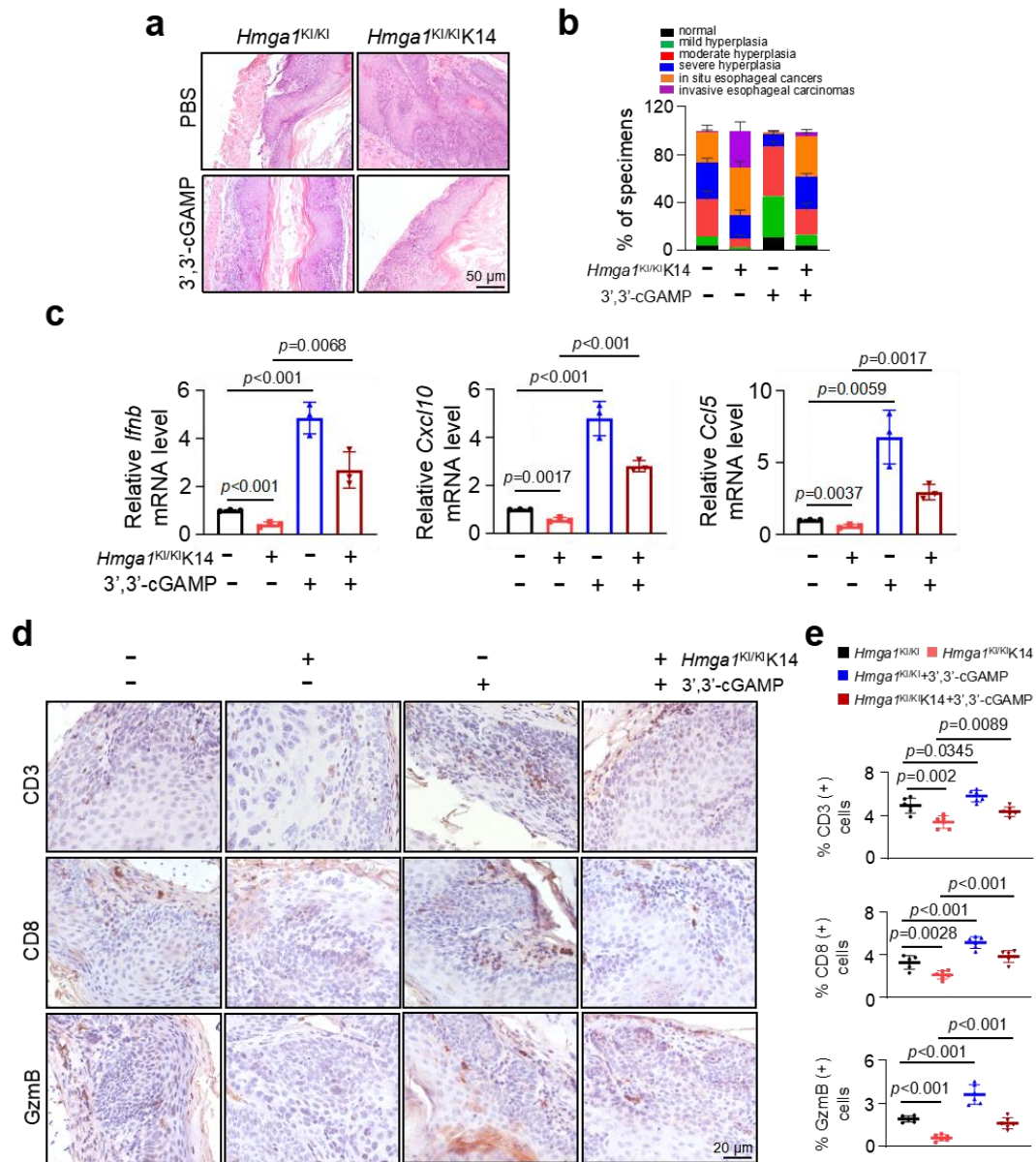


**Supplementary Fig. 24 HMGA1 knockdown enhances the anti-tumor effect of DMXAA, a STING agonist, on syngeneic mouse allografts from murine AKR cells.** Murine ESCC AKR cells with or without HMGA1 knockdown were subcutaneously transplanted into C57BL/6 mice. DMXAA (25 mg/kg) was administered by intraperitoneal injection into the mice every other day from day 2 post-transplantation. **a** Schematic outline of DMXAA treatment. The schematic diagram were created using Microsoft Office PowerPoint 2019. **b** Representative images of subcutaneous tumors. **c** Volume of subcutaneous tumors. **d** Tumor weight at the time of sacrifice. **e, f** Representative IHC images and quantitation of CD3, CD8, and GzmB in tumors. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**c, d, f**). Sample sizes: (**b-f**) n=5 independent mice. Image in **e** shows representative results from three independent experiments. Source data are provided in the Source Data file.



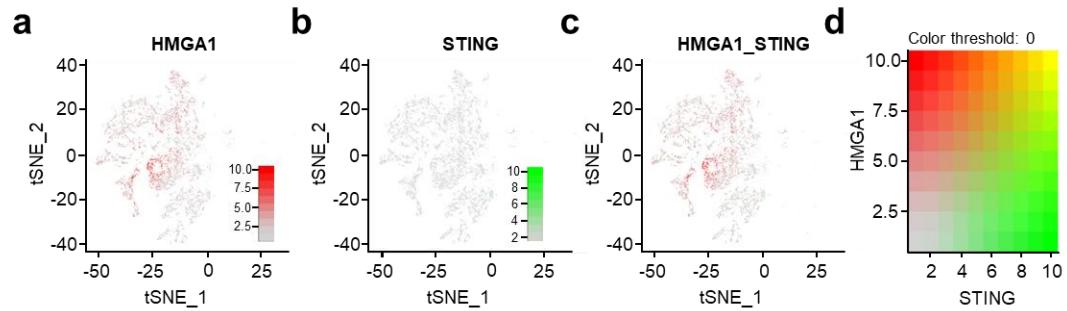
**Supplementary Fig. 25 Knock-out of HMGA1 promotes upregulation of inflammatory cytokines in STING agonists 3'3'-cGAMP-treated murine orthotopic ESCCs.** *Hmga1*<sup>flox/flox</sup> and *Hmga1*<sup>flox/flox</sup>K14 mice were treated with 80 mg/L 4NQO in drinking water for a total of 5 months. Starting from the first day of the third month, mice were injected intravenously (i.v.) with 100  $\mu$ L of PBS or PBS containing 10  $\mu$ g of 3'3'-cGAMP and 3  $\mu$ L of Lipofectamine 2000 every three days for 3 months. **a** Schematic diagram for 3'3'-cGAMP treatment. The schematic diagram were created using Microsoft Office PowerPoint 2019. **b** Levels of *Ifnb*, *Cxcl10*, and *Ccl5* in esophageal tissues from the mice by qPCR analysis. **c** Representative IHC images and quantitation of CXCL10 and CCL5 in esophageal tissues from 4NQO-induced mice with or without 3'3'-cGAMP treatment. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**b**, **c**). Sample sizes: (**b**) n = 3; (**c**) n = 6 independent mice. Image in **c**

shows representative results from three independent experiments. Source data are provided in the Source Data file.

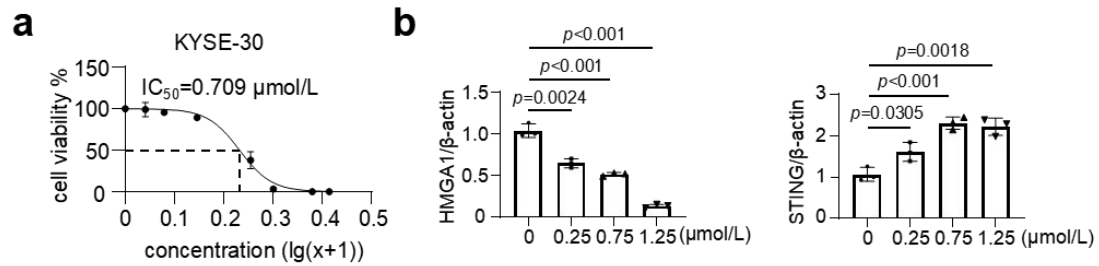


**Supplementary Fig. 26 HMGA1 expression negatively impacts the anti-tumor effect of STING agonists on murine orthotopic ESCCs.** *Hmga1*<sup>KI/KI</sup> and *Hmga1*<sup>KI/KI</sup>K14 mice were treated with 80 mg/L 4NQO in drinking water for a total of 5 months. Starting from the first day of the third month, mice were injected intravenously (i.v.) with 100  $\mu$ L of PBS or PBS containing 10  $\mu$ g of 3',3'-cGAMP and 3  $\mu$ L of Lipofectamine 2000 every three days for 3 months. **a** Representative HE staining of esophageal tissues from the mice. Scale bar: 50  $\mu$ m. **b** Percentages of pathological

alterations in esophageal tissues from the mice. **c** Levels of *Ifnb*, *Cxcl10*, and *Ccl5* in esophageal tissues from the mice by qPCR analysis. **d, e** Representative IHC staining and quantitation of CD3, CD8, and GzmB in esophageal tissues from 4NQO-treated mice. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**c, e**). Sample sizes: (**a, b, d, e**)  $n = 6$ ; (**c**)  $n = 3$  independent mice. Image in **a, d** shows representative results from three independent experiments. Source data are provided in the Source Data file.

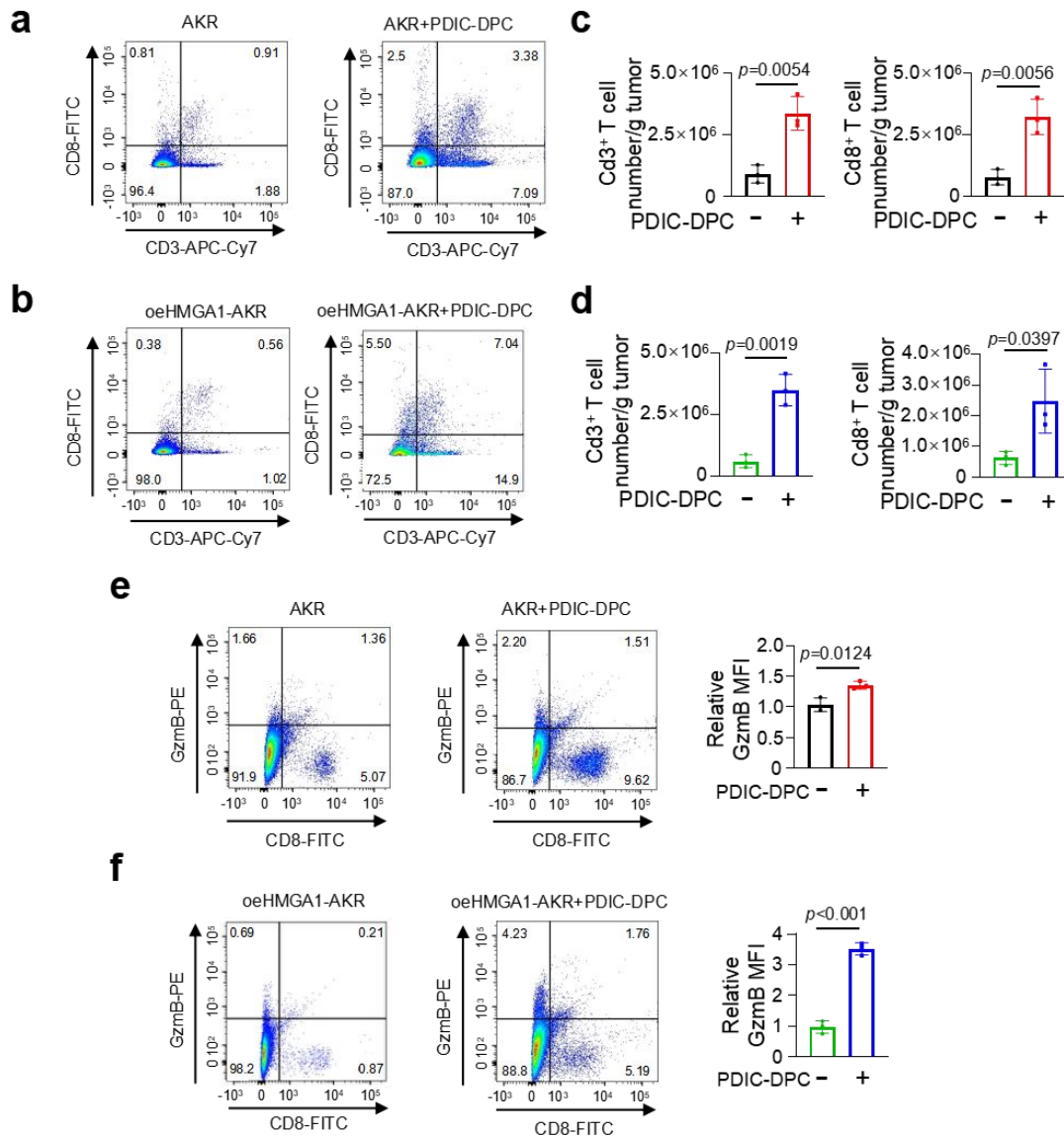


**Supplementary Fig. 27 Expression of HMGA1 and STING in esophageal epithelia in ESCC patients.** **a-d** The t-SNE maps show the expression patterns of HMGA1 (**a**, red) and STING (**b**, green), as well as their merged expression (**c**) in epithelial cells from ESCC patients, based on scRNA-seq data (GSE188900). Panel **d** indicates the color threshold applied in **c**. HMGA1 is predominantly expressed in tumor epithelial cells, whereas STING exhibits minimal expression in these cells within the dataset (GSE188900).



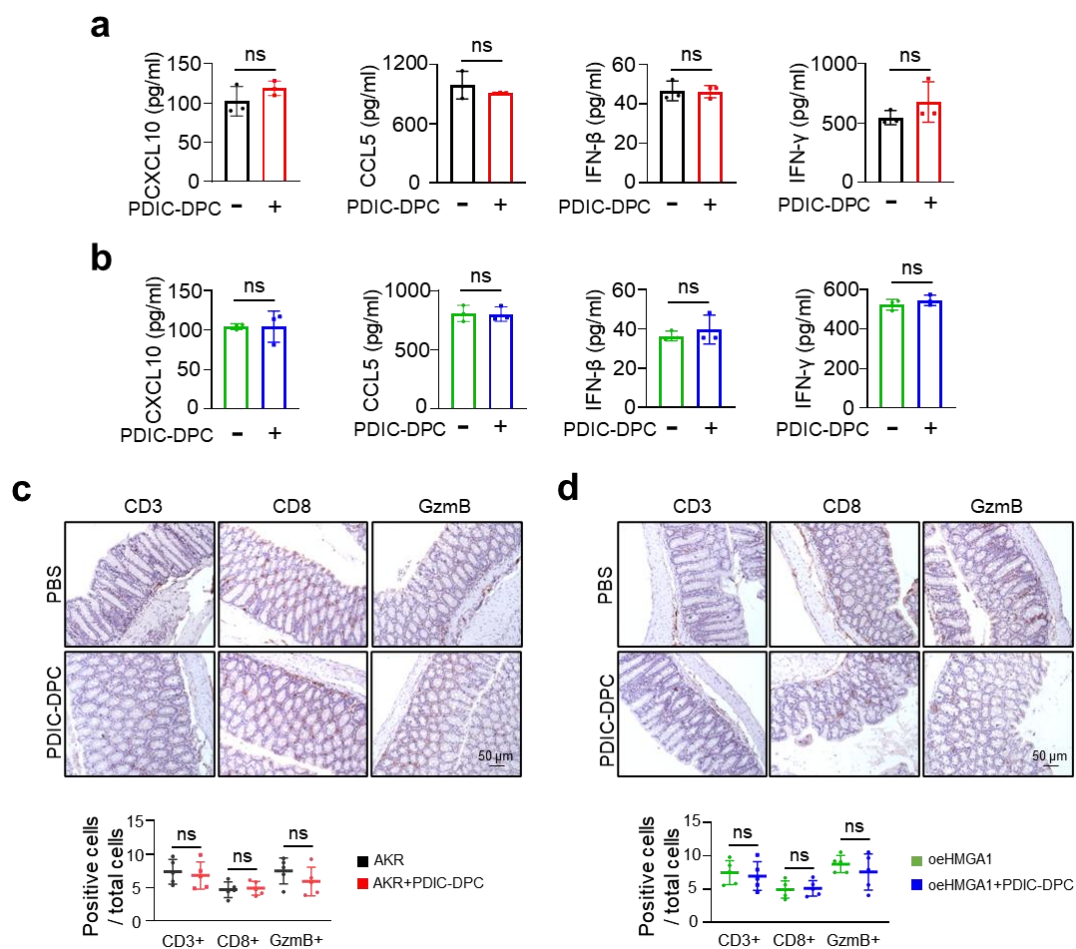
**Supplementary Fig. 28 PDIC-DPC inhibits the expression of HMGA1 in ESCC**

**cells. a** KYSE-30 cells were treated with varying concentrations of PDIC-DPC (0, 0.1, 0.2, 0.4, 0.8, 1, 1.4, 1.6 μmol/L) for 48 hours. Cell viability was assessed using CCK8, and IC<sub>50</sub> values were determined through curve fitting analysis in GraphPad Prism software 8. **b** The expression of HMGA1 in PDIC-DPC-treated AKR cells was quantified from western blot data shown in Fig. 8d. Data are expressed as mean ± SD. Statistical significance was determined by two-tailed unpaired t-test (**b**). Sample sizes: (**a, b**) n = 3 independent experiments. Source data are provided in the Source Data file.

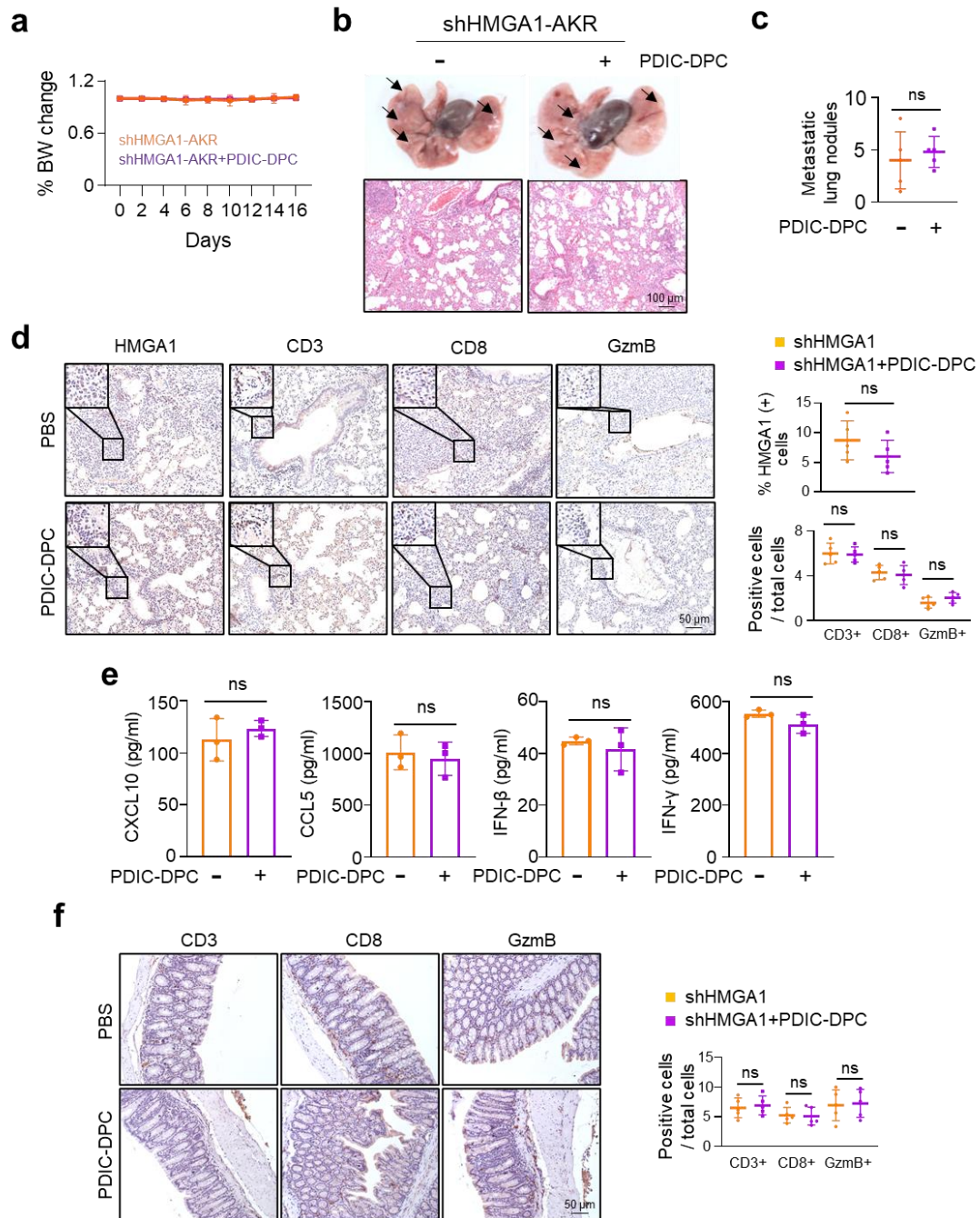


**Supplementary Fig. 29 HMGA1 inhibitor PDIC-DPC promotes T lymphocyte infiltration in lung metastatic foci established from AKR and oeHMGA1-AKR cells.** Pulmonary metastasis models were established by intravenous injection (i.v.) of AKR and oeHMGA1-AKR cells. Mice were administered with PBS or PDIC-DPC (2 mg/kg) by i.v. injection every 3 days. Lungs were harvested 16 days post-injection for analysis. **a, b** CD3<sup>+</sup>/CD8<sup>+</sup> T cells in lung metastatic tissues were analyzed by flow cytometry. **c, d** The number of CD3<sup>+</sup> and CD8<sup>+</sup> T cells in lung metastatic tissues was measured by flow cytometry. **e, f** Expression of GzmB in CD8<sup>+</sup> T cells was measured

and quantified by flow cytometry. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**c-f**). Sample sizes: (**a-f**)  $n = 3$  independent mice. Image in **a, b, e, f** shows representative results from three independent experiments. Source data are provided in the Source Data file.



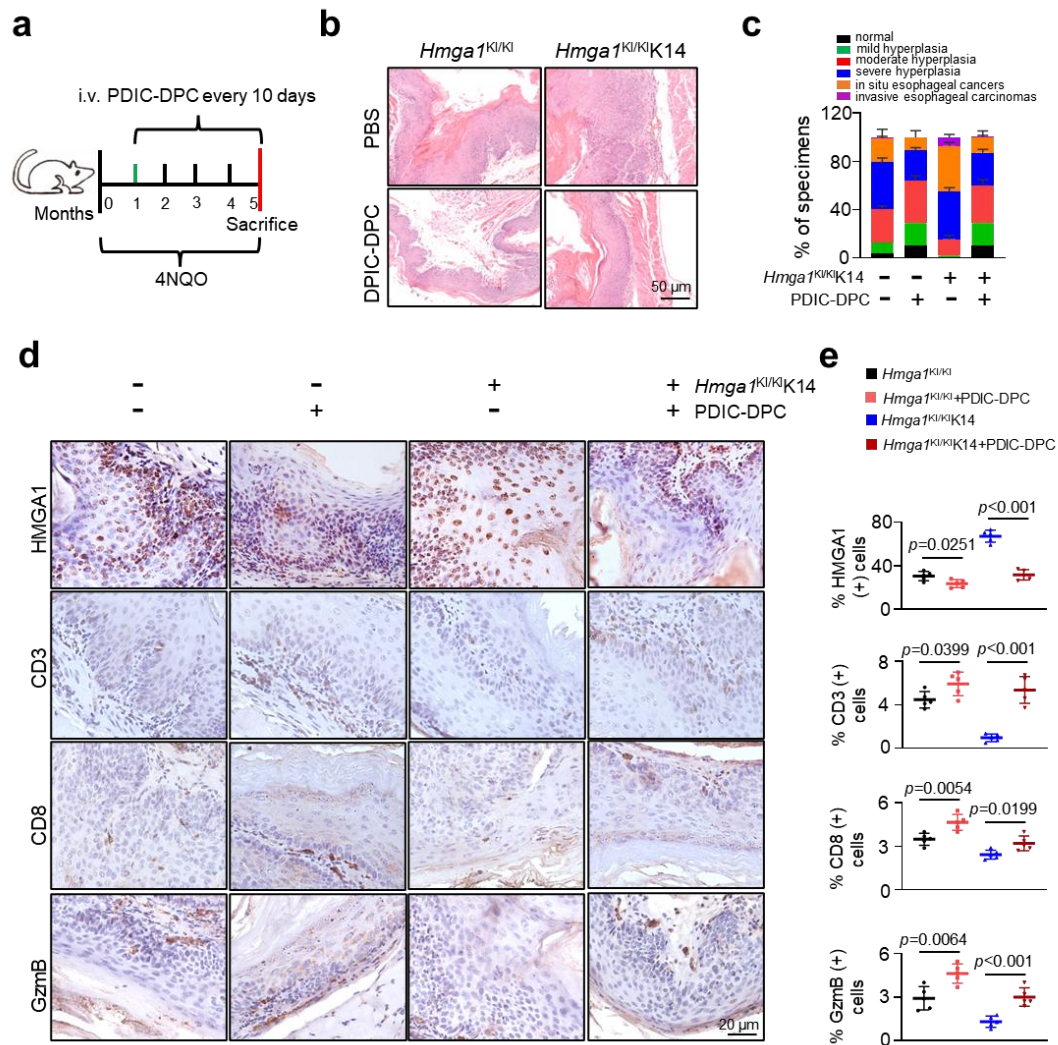
**Supplementary Fig. 30 HMGGA1 inhibitor PDIC-DPC does not affect the whole body immunity of the mice.** **a, b** Serum levels of CXCL10, CCL5, IFN- $\beta$ , and IFN- $\gamma$  in PDIC-DPC-treated mice were detected using ELISA kits. **c, d** Expression of CD3, CD8, and GzmB in colorectal tissue from PDIC-DPC-treated mice was analyzed by IHC. Representative images (upper panel) and quantitations (bottom panel) are shown. Scale bar: 50  $\mu$ m. ns, no statistical difference. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a-d**). Sample sizes: (**a, b**)  $n = 3$ ; (**c, d**)  $n = 5$  independent mice. Image in **c, d** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 31 Marginal effect of PDIC-DPC on lung metastases**

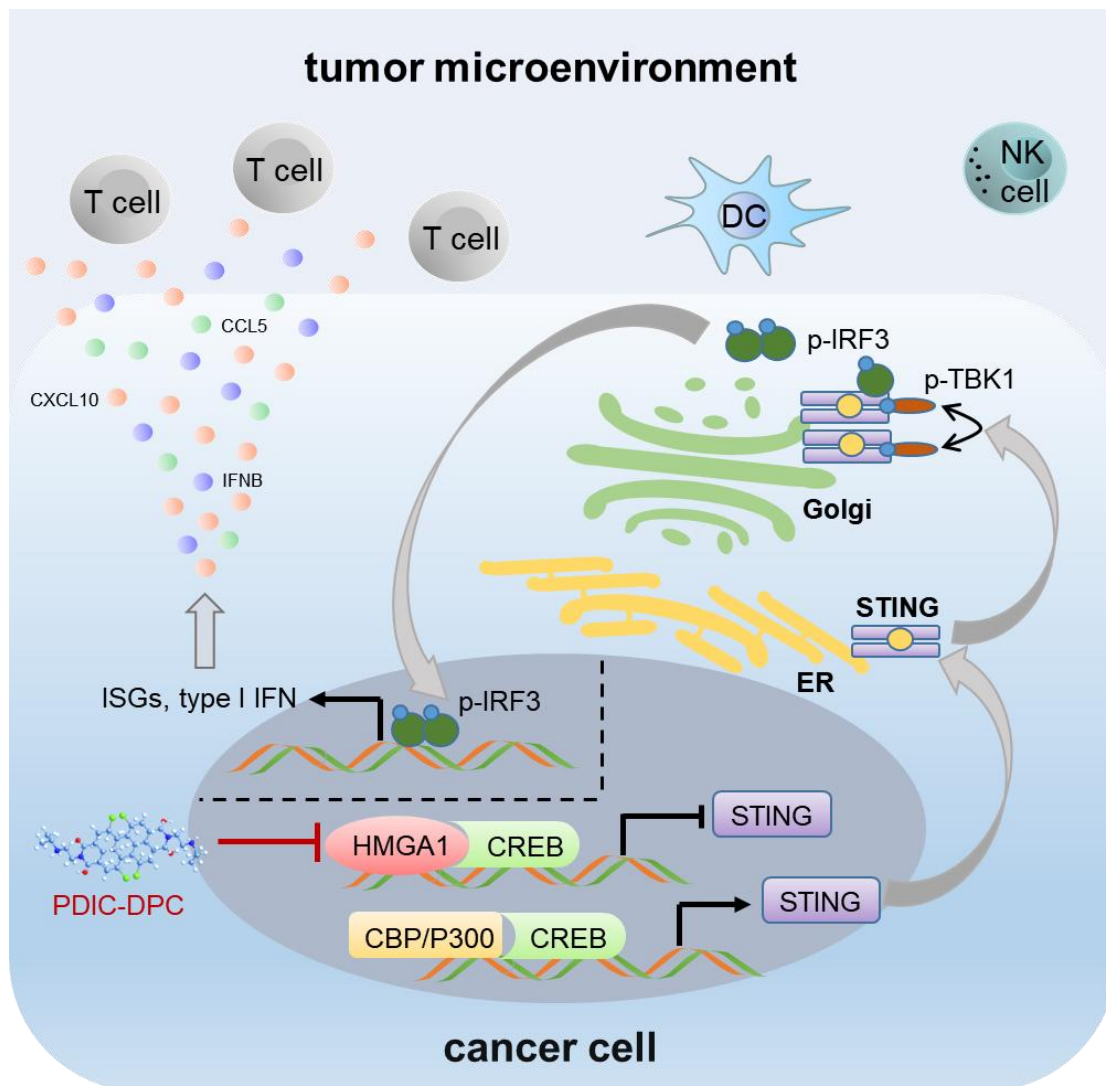
**established by shHMGA1-AKR cells.** Pulmonary metastasis model was established by injecting shHMGA1-AKR cells ( $5 \times 10^5$  cells) into C57BL/6J mice intravenously (i.v.). PBS and PDIC-DPC (2 mg/kg) were administrated every 3 days. Mice were sacrificed on day 16 post-injection of AKR cells and lungs of the mice were then harvested for the analyses. **a** Body weight (BW) of mice. **b** Representative images of

isolated lungs and HE staining of lung sections. Images of lungs from mice showing histological examination with HE staining. Scale bar: 100  $\mu$ m. **c** Number of metastatic lung nodules. Bar graph quantifying the number of metastatic lung nodules in mice treated with either PBS or PDIC-DPC. **d** Representative IHC staining and quantitation of HMGA1, CD3, CD8, and GzmB in lung metastatic tissues. Scale bar: 50  $\mu$ m. **e** Contents of CXCL10, CCL5, IFN- $\beta$ , and IFN- $\gamma$  in the serum. Bar graph showing levels of CXCL10, CCL5, IFN- $\beta$ , and IFN- $\gamma$  in the serum of PDIC-DPC-treated mice, measured by ELISA. **f** Representative IHC staining and quantitation of CD3, CD8, and GzmB in colorectal tissue of PDIC-DPC-treated mice. Scale bar: 50  $\mu$ m. ns, no statistical difference. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**a**, **c**, **d**, **e**, **f**). Sample sizes: (**a-d**, **f**)  $n = 5$ ; (**e**)  $n = 3$  independent mice. Image in **b**, **d**, **f** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 32 PDIC-DPC alleviates malignant progression of orthotopic ESCC by inhibiting the expression of HMGA1.** *Hmga1*<sup>KI/KI</sup> and *Hmga1*<sup>KI/KI</sup>K14 mice were treated with 80 mg/L 4NQO in drinking water for a total of 5 months. From the first day of the 2<sup>nd</sup> month, the mice were injected intravenously (i.v.) with 100  $\mu$ L PBS or PDIC-PDC (2 mg/kg in 100  $\mu$ L PBS) every 10 days for 4 months. **a** Schematic diagram for 4NQO-induced ESCC and treatment of PDIC-DPC. The schematic diagram were created using Microsoft Office PowerPoint 2019. **b** Representative HE staining of esophageal tissues from 4NQO-induced mice treated with or without PDIC-DPC. Scale bar: 50  $\mu$ m. **c** Percentages of pathological

alterations in esophageal tissues from 4NQO-induced mice treated with or without PDIC-DPC. **d, e** Representative IHC staining (**d**) and quantitation (**e**) of HMGA1, CD3, CD8, and GzmB in esophageal tissues from 4NQO-treated mice with or without PDIC-DPC intervention. Scale bar: 20  $\mu$ m. Data are expressed as mean  $\pm$  SD. Statistical significance was determined by two-tailed unpaired t-test (**e**). Sample sizes: **(b-e)** n = 5 independent mice. Image in **b, d** shows representative results from three independent experiments. Source data are provided in the Source Data file.



**Supplementary Fig. 33 Schematic Diagram of HMGA1 in the Promotion of ESCC Progression by Inhibiting STING Expression.** In ESCC, HMGA1 is highly expressed and represses STING transcription by competing with the coactivator CBP/p300 for binding to CREB. Inhibition of HMGA1 leads to enhanced STING transcription, which activates the STING-TBK1-IRF3 signaling pathway. This activation promotes the nuclear translocation of IRF3, increases the transcription of interferon-stimulated genes (ISGs), and enhances T lymphocyte infiltration into tumors, resulting in more effective tumor cell killing. The HMGA1 inhibitor PDIC-DPC mitigates the repressive effects of HMGA1, thereby facilitating greater immune cell

infiltration into ESCCs and potentially improving anti-tumor responses. The three-dimensional structure of PDC-DPC in the figure was generated using AutoDock Vina 4.2.6, while the remaining illustrations were created using Microsoft Office PowerPoint 2019.

## Supplementary tables

**Table 1. KEGG enrichment analysis of immune system related genes**

| Upregulated gene                                                                                                                                                                                                  | Down-regulated gene                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PAK1, RPS6KB, PIK3R, SPHK, GAB2, SHIP2, JNK, SOS, PIK3R2, AKT, JAK2, PTK2, ADRBK, PREX1, ARRB, ADCY7, SPP1, IKBKE, CBL, COL3A, ITGA2, OTUD5, DUBA, ANK, TXK, CTNNB1, KITLG, ITGA1, CD46, CTSS, CREB1, CANX, DNM1L | ADAR, MAVS, IPS1, IKBKB, RPB8, POLR2H, HSP90A, ATG16L, BIRC2_3, TNFAIP3, DHX33, BCL2L1, TYK2, FOSB, MAP3K1, IL6R, IL1RAP, BTRC, GSK3A, ARRB, PAK1, TIAM1, GRK4_5_6, PDPK1, SPHK, HSPA1_8, MCP, CD44, AF6 |

**Table 2. Primer sequences for qRT-PCR analysis and siRNAs/shRNAs for gene knockdown**

### 1. Primers used in qPCR analysis

| Gene                 | Primer sequences (5' to 3') |
|----------------------|-----------------------------|
| homo IFIT1-F         | TTGATGACGATGAAATGCCTGA      |
| homo IFIT1-R         | CAGGTCACCAGACTCCTCAC        |
| homo IFIT2-F         | GGTCTCTTCAGCATTTATTGGTG     |
| homo IFIT2-R         | TGCCGTAGGCTGCTCTCCA         |
| homo IFIT3-F         | GAACATGCTGACCAAGCAGA        |
| homo IFIT3-R         | CAGTTGTGTCCACCCTTCCT        |
| homo IFN- $\beta$ -F | GCCTCAAGGACAGGATGAAC        |
| homo IFN- $\beta$ -R | AGTCTCATTCCAGCCAGTGC        |
| homo CXCL10-F        | GTGGCATTCAAGGAGTACCTC       |

|                     |                          |
|---------------------|--------------------------|
| homo CXCL10-R       | TGATGGCCTTCGATTCTGGATT   |
| homo CCL5-F         | CCAGCAGTCGTCTTTGTCAC     |
| homo CCL5-R         | CTCTGGGTTGGCACACACTT     |
| mus IFN- $\beta$ -F | CTGGCTTCCATCATGAACAA     |
| mus IFN- $\beta$ -R | AGAGGGCTGTGGTGGAGAA      |
| mus CXCL10-F        | ATCATCCCTGCGAGCCTATCCT   |
| mus CXCL10-R        | GACCTTTTTTGGCTAAACGCTTTC |
| mus CCL5-F          | CAAGTGCTCCAATCTTGCAAGTC  |
| mus CCL5-R          | TTCTCTGGGTTGGCACACAC     |
| mus CD3-F           | ATGCGGTGGAACACTTTCTGG    |
| mus CD3-R           | GCACGTCAACTCTACACTGGT    |
| mus CD8-F           | AAGAAAATGGACGCCGAAGTT    |
| mus CD8-R           | AAGCCATATAGACAACGAAGGTG  |
| mus GzmB-F          | ATGAAGATCCTCCTGCTACT     |
| mus GzmB-R          | TTCTGTACTGTCAGCTCAAC     |

## 2. Primers used in ChIP-qPCR analysis

| Name | Forward Primer         | Reverse Primer         |
|------|------------------------|------------------------|
| CHIP | GCTCCTACCTAATATCATCCCC | AGTTATTTCCGGTAACAAGAGC |

## 3. Primers used in vector construction

| Gene    | Forward Primer                               | Reverse Primer                               |
|---------|----------------------------------------------|----------------------------------------------|
| oeHMGA1 | GGACCGGTTCTAGAGCCACC<br>ATGAGTGAGTCGAGCTCGAA | TCTGGAACATCGTATGGGTA<br>CTGCTCCTCCTCCGAGGACT |
| oeSTING | GGACCGGTTCTAGAGCCACCA<br>TGCCCCACTCCAGCCTGCA | TCTGGAACATCGTATGGGTAA<br>GAGAAATCCGTGCGGAGAG |
| oeCREB  | GGACCGGTTCTAGAGCCACC<br>ATGACCATGGAATCTGGAGC | TCTGGAACATCGTATGGGTAT<br>TAATCTGATTTGTGGCAGT |

|                   |                                        |                                         |
|-------------------|----------------------------------------|-----------------------------------------|
| STING-Promoter-P1 | GGTACCGAGCTCTTACAGAG<br>GGCAAATTGTCTAT | CTTAGATCGCAGATTTGTAAT<br>CCTCGCACTTTGGG |
| STING-Promoter-P2 | GGTACCGAGCTCTTCCAAAG<br>TGCGAGGATTACAA | CTTAGATCGCAGATAGTTATT<br>TCCGGTAACAAGAG |
| STING-Promoter-P3 | GGTACCGAGCTCTTGCCTC<br>AGCCTCCCAAGTAG  | CTTAGATCGCAGATTGCTGG<br>GAAGGAGGGTATTT  |
| STING-Promoter-P4 | GGTACCGAGCTCTTAAAGGG<br>GAACTGGGAGGAAG | CTTAGATCGCAGATGCAAGC<br>ATCCAAGTGAAGGG  |

#### 4. Sequences of shRNAs for knocking down genes

| Target    | Sense strand          |
|-----------|-----------------------|
| shHMGA1-1 | GAAGTGCCAACACCTAAGAGA |
| shHMGA1-2 | TGAGTGAGTCGAGCTCGAAGT |
| shSTING   | GCATTACAACAACCTGCTACG |
| shNC      | GTTCTCCGAACGTGTCACGT  |

#### 5. Sequences of siRNAs for knocking down genes

| Target  | Sense strand          | Antisense strand       |
|---------|-----------------------|------------------------|
| siSTING | CCGGAUUCGAACUUACAAUTT | AUUGUAAGUUCGAAUCCGGTT  |
| siGAS   | GGCCUCUGCUUUGAUAACUTT | AGUUAUCAAAGCAGAGGCCTT  |
| siP300  | CCAUGAAUCCAGGGCCUAATT | UUAGGCCCUUGGAUUCAUGGTT |
| siNC    | UUCUCCGAACGUGUCACGUTT | ACGUGACACGUUCGGAGAATT  |

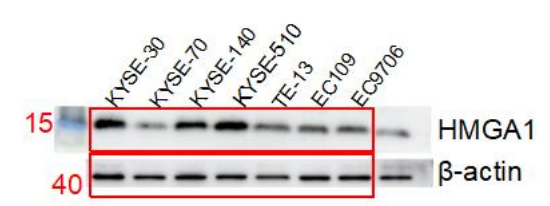
**Table 3. Primary antibodies used in this study.**

| Antibody | Company (Cat. No.)     | Working dilutions                 |
|----------|------------------------|-----------------------------------|
| HMGA1    | Abcam (ab129153)       | WB: 1:10,000; IHC: 1:500          |
| HMGA1    | Abcam (ab252930)       | ChIP: 1:50                        |
| HMGA1    | Santa Cruz (sc-393213) | WB: 1/1,000; IHC:1:400; IP: 1:200 |

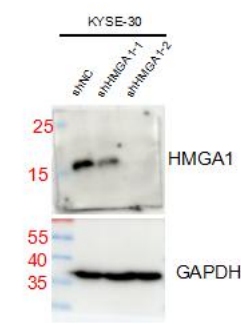
|                    |                                     |                                   |
|--------------------|-------------------------------------|-----------------------------------|
| STING              | Cell Signaling Technology (#13647)  | WB: 1:1,000; IHC: 1:200; IP: 1:50 |
| p-STING            | Cell Signaling Technology (#50907S) | WB: 1:1,000                       |
| TBK1               | Cell Signaling Technology (#3504)   | WB: 1:1,000                       |
| p-TBK1             | Cell Signaling Technology (#5483)   | WB: 1:1,000                       |
| IRF3               | Proteintech (11312-1-AP)            | WB: 1:1,000; IF: 1:100            |
| p-IRF3             | Cell Signaling Technology (#4947)   | WB: 1:1,000                       |
| CREB               | Cell Signaling Technology (#9197)   | WB: 1:1,000; IP: 1:50; ChIP: 1:50 |
| cGAS               | Santa Cruz (sc-515777)              | WB: 1:1,000                       |
| p300               | Santa Cruz (sc-32244)               | WB: 1:1,000                       |
| AKT                | Cell Signaling Technology (#4691)   | WB: 1:1,000                       |
| p-AKT              | Cell Signaling Technology (#4060)   | WB: 1:1,000                       |
| mTOR               | Cell Signaling Technology (#2983)   | WB: 1:1,000                       |
| p-mTOR             | Cell Signaling Technology (#5536)   | WB: 1:1,000                       |
| PI3K p85 $\alpha$  | Proteintech (60225-1-Ig)            | WB: 1:1,000                       |
| PI3K p110 $\alpha$ | Proteintech (67071-1-Ig)            | WB: 1:1,000                       |
| CXCL10             | Proteintech (10937-1-AP)            | IHC: 1:200                        |
| CCL5               | Proteintech (12000-1-AP)            | IHC: 1:100                        |
| CD3                | Abcam (ab16669)                     | WB: 1:1,000; IHC: 1:150           |
| CD8                | Abcam (ab217344)                    | WB: 1:1,000; IHC: 1:500           |
| GZMB               | Santa Cruz (sc-8022)                | WB: 1:1,000; IHC: 1:200           |
| $\beta$ -actin     | Proteintech (66009-1-Ig)            | WB: 1/10,000                      |
| GAPDH              | Proteintech (60004-1-Ig)            | WB: 1/50,000                      |

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Supplementary Fig. 1a. Uncropped scans.



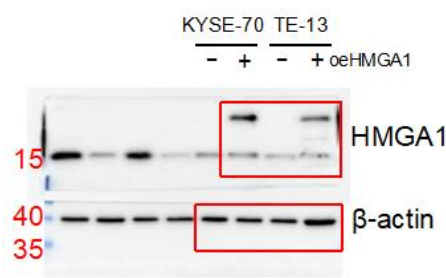
Supplementary Fig. 1c. Uncropped scans.



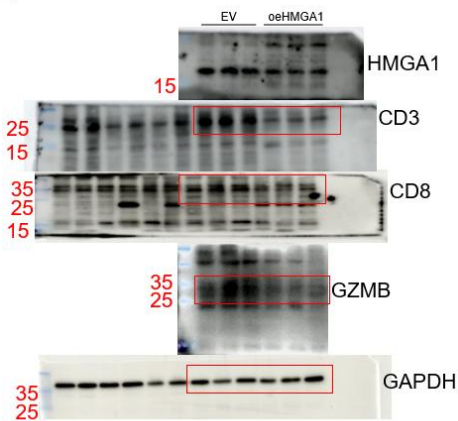
Supplementary Fig. 1e. Uncropped scans.



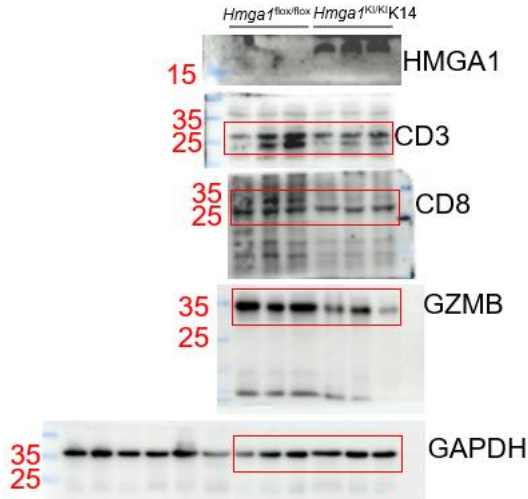
Supplementary Fig. 1g. Uncropped scans.



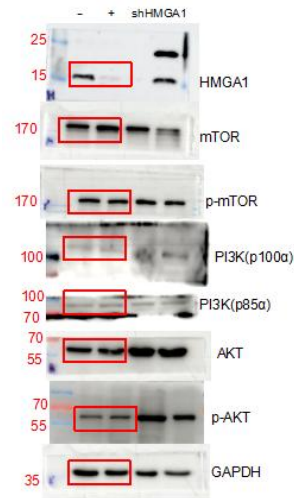
Supplementary Fig. 5e. Uncropped scans.



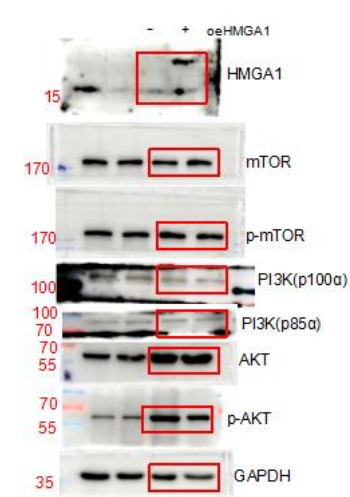
Supplementary Fig. 7c. Uncropped scans.



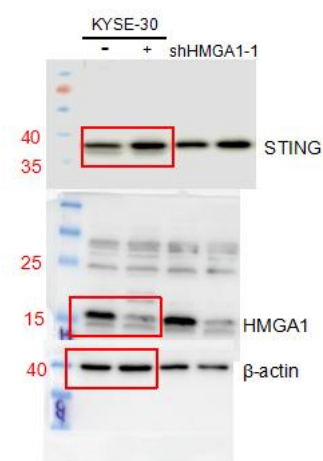
Supplementary Fig. 10g. Uncropped scans.



Supplementary Fig. 10h. Uncropped scans.



Supplementary Fig. 13e. Uncropped scans.



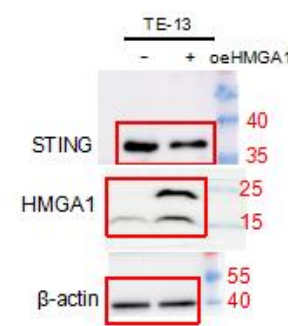
Supplementary Fig. 13f. Uncropped scans.



Supplementary Fig. 13g. Uncropped scans.



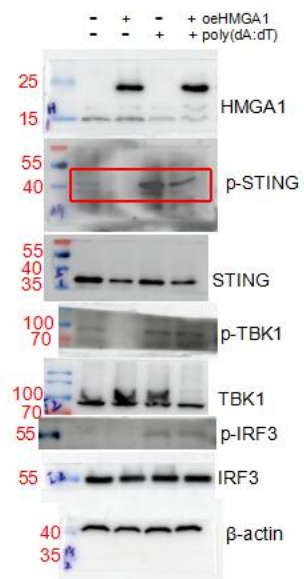
Supplementary Fig. 13h. Uncropped scans.



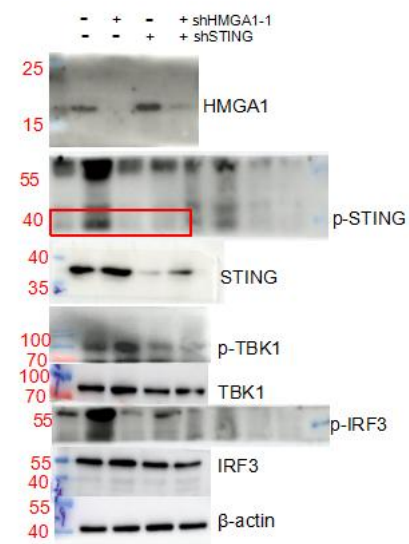
Supplementary Fig. 14a. Uncropped scans.



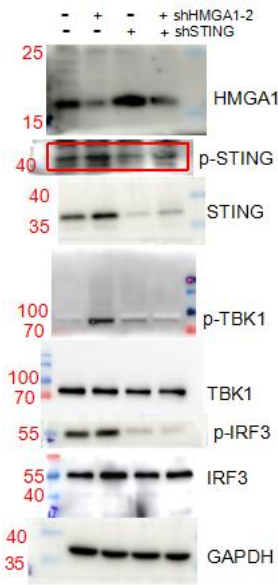
Supplementary Fig. 14f. Uncropped scans.



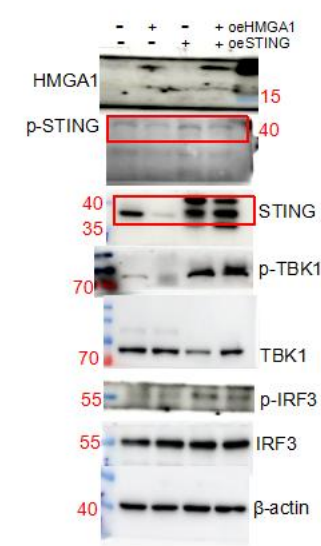
Supplementary Fig. 15b. Uncropped scans.



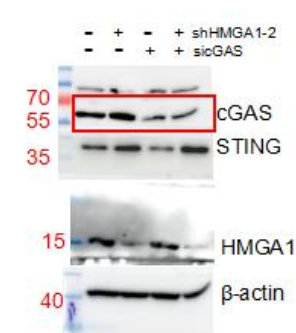
Supplementary Fig. 15c. Uncropped scans.



Supplementary Fig. 16b. Uncropped scans.



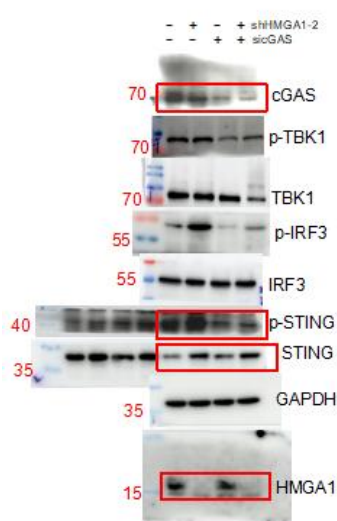
Supplementary Fig. 18b. Uncropped scans.



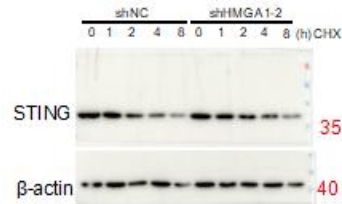
Supplementary Fig. 18c. Uncropped scans.



Supplementary Fig. 18d. Uncropped scans.



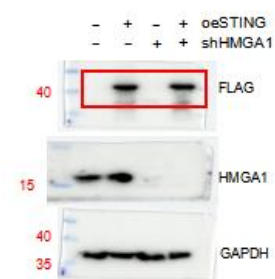
Supplementary Fig. 19a. Uncropped scans.



Supplementary Fig. 19b. Uncropped scans.



Supplementary Fig. 19c. Uncropped scans.



Supplementary Fig. 21e. Uncropped scans.

