

LEGENDS TO SUPPLEMENTAL FIGURES

Suppl. Figure 1: MDM2 accumulation inhibits RNA Pol III activity

(A) *Left*: Quantification of MDM2, p53 and p21 protein levels normalized to GAPDH and shown for three independent replicates $\pm$ SEM. *Right*: Immunoblot analyses of SJSA-1 cells treated with Nutlin (20 μ M), MI-1061 (1 μ M) and MD-224 (1 μ M) for 12 h. Replicates of the results presented in Fig. 1B.

(B) Metabolic pulse-labeling of nascent RNAs at multiple time points following the addition of **Nutlin (20 μ M)**, MI-1061 (1 μ M) or MD-244 (1 μ M). Independent replicates corresponding to Fig. 1D.

(C) Binding sites of the primers used for RT-qPCR analyses of tRNAs and their precursors in Fig. 1, E and F. The whole tRNA sequences were taken from the Genomic tRNA Database (GtRNAdb). Capital letters indicate exon sequences, whereas lowercase letters represent introns.

(D) RNA Pol III transcripts in GOT-3 cells. Levels of total and non-spliced *tRNA Leu* and *tRNA Tyr* and the p53 target genes *MDM2* and *CDKN1A* were quantified by RT-qPCR upon treatment with 20 μ M of Nutlin for 24 h prior to RNA harvesting. Graphs represent means of three independent replicates $\pm$ SEM.

(E) 93T449 cells were treated for 6h with 20 μ M of Nutlin, and RT-qPCR analysis was performed to quantify the expression of the p53 target genes *MDM2* and *CDKN1A*, and RNA Pol III transcripts. Total and unspliced *tRNA Leu* and *tRNA Tyr* were suppressed upon MDM2 induction. Graphs represent means of three independent replicates $\pm$ SEM.

(F) Representative images of O-propargyl-puromycin (OPP) labeling to visualize protein synthesis in SJSA-1 cells. Cells were treated as described in (A) for 14 h, followed by OPP labeling (0.05 mM) for 2 h prior to fixation and staining with Azide-Fluor 488. Untreated cells subjected to OPP labeling served as a positive control (pos. Ctrl), whereas cells without OPP treatment (neg. Ctrl) or without secondary staining served as negative controls. In addition, cells were treated with the translation inhibitor cycloheximide (50 μ g/mL) for 15 min prior to OPP labeling. Scale bar: 30 μ m

(G) Quantification of nuclear OPP fluorescence intensity shown in (F) using 4',6-diamidino-2-phenylindole (DAPI) to define the region of interest (ROI) masks; red lines indicate the mean for each condition.

(H) Representative images of OPP labeling in H1299 cells. Cells were overexpressed with MDM2 or an empty control plasmid for 48h, followed by OPP labeling (0.05 mM) for 2 h prior to fixation and staining with Azide-Fluor 488. Cells were subsequently stained for MDM2 by

immunofluorescence. Cells without OPP treatment or treated with cycloheximide (50 µg/mL) for 15 min prior to OPP labelling served as negative controls. Scale bar: 30 µm

(I) Quantification of nuclear OPP fluorescence intensity shown in (H) using 4',6-diamidino-2-phenylindole (DAPI) or the red MDM2 signal (for MDM2 overexpression) to define the region of interest (ROI) masks; red lines indicate the mean for each condition.

(J) RNA Polymerase I transcripts in SJSA-1 cells. Levels of 28S and 45S *rRNA* were quantified by RT-qPCR upon treatment with 1 µM of either MI-1061 or MD-224, or with 20 µM of Nutlin, 12 or 24 h prior to RNA harvest. Graphs represent means of three independent replicates ± SEM.

Statistical analyses: unpaired t-test; ns not significant; *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Suppl. Figure 2: MDM2 binds to POLR3A, the catalytical subunit of RNA Pol III, and inhibits its binding to Pol III target genes

(A) Representative PLA negative control images. Only a single primary antibody was applied to assess nonspecific amplification; no PLA signal was detected. Scale bar: 30 µm. For quantification cf. Fig. 2A.

(B) Immunoblot analysis of whole-cell lysates from SJSA-1 cells treated overnight with 20 µM Nutlin, with 20 µM MG-132 added for the final 4 hours before harvest.

(C) *Left*: Representative PLA images to verify assay specificity. MDM2 was siRNA-depleted, and SJSA-1 cells were treated with 20 µM Nutlin for 6 h. Scale bar: 30 µm. *Right*: Quantification of nuclear PLA fluorescence intensity using DAPI masks; red lines indicate the mean for each condition.

(D) Co-immunoprecipitation (Co-IP) of endogenous POLR3A with MDM2 in SJSA-1 cells treated overnight with 20 µM Nutlin, with 20 µM MG-132 added for the final 4 hours before harvest. Immunoprecipitation was performed using an anti-POLR3A antibody. An anti-β-galactosidase antibody served as a negative control; cf. Fig. 2B.

(E) Lack of MDM2 occupancy at canonical RNA Pol III promoter sites in SJSA-1 Cas9 cells treated with 20 µM Nutlin, 1 µM MI-1061, or 1 µM MD-224 for 8 h, assessed by chromatin immunoprecipitation (ChIP) and amplification of the indicated promoter regions. An intragenic region within the *ARPP0* gene and an intergenic region with low POLR3A occupancy (neg. Ctrl) were amplified as negative controls. Background precipitation by pre-immune IgG (average) is indicated by a dotted line; cf. Fig. 2D.

Suppl. Figure 3: Mapping the interaction between MDM2 and POLR3A

(A) Analysis of MDM2–POLR3A interactions by proximity ligation assay (PLA). Representative PLA images. Scale bar, 100 μ m. **(A)** Co-expression of POLR3A with MDM2-fragment 298-491 or wild-type (wt) MDM2, stained with 4B11 antibody. **(B)** Co-expression of POLR3A with MDM2 (fragment 6–200) or wt MDM2, stained with antibody IF2. Quantification of images shown in Fig. 3D.

(C) Representative PLA positive and negative controls. Positive control: MDM2 and p53 overexpression. Negative controls: only a single primary antibody or no PLA probe to assess nonspecific amplification. Scale bar, 100 μ m.

(D) Quantification of fluorescence intensity per nucleus, using DAPI staining as a mask. Red lines indicate the mean fluorescence for each control condition.

Suppl. Figure 4: poly(dA:dT) induces innate immune-response proteins and cytokine release

(A) SJSA-1 cells transfected with 100 ng/mL poly(dA:dT) for 2 to 24 hours to monitor poly(dA:dT) uptake. Representative DAPI images are shown. Arrows indicate DNA clusters in the cytoplasm, reflecting poly(dA:dT). Scale bar: 30 μ m

(B) Mass-Spectrometry-based protein identification and quantification. Volcano plot showing $\log_2$ (fold change) vs $-\log_{10}$ (p-value) for all quantified proteins. Significantly regulated proteins (p-value < 0.05, $|\log_2\text{FC}| \geq 0.8$) are highlighted in blue (downregulated) and red (upregulated). *Left:* SJSA-1 cells were treated with DMSO or 20 μ M Nutlin for 36 hours. *Right:* Cells were treated with Nutlin (20 μ M) for 36 hours and then transfected or not with 100 ng/mL poly(dA:dT) for the last 24 hours. Suppl. Table 2 contains all input mass-spectrometry candidates; cf. Fig 4A.

(C) Cytokine release from SJSA-1 cells after 36 hours of treatment with 1 μ M MI-1061 or 1 μ M MD-224, and/or 100 ng/mL poly(dA:dT) transfection for the last 24 hours, as determined by membrane-based antibody arrays; cf. Fig. 4C.

Suppl. Figure 5: MDM2 represses the inflammatory response.

(A) Expression of *IFIT1*, *IFIT2*, and *IFNB* in SJSA-1 cells following RIG-I, IRF3, or POLR3A knockdown, combined with transfection of 25 or 100 ng/mL poly(dA:dT) for the last 24 h. Graphs represent means of three independent replicates $\pm$ SEM. **Expression levels of ISGs**

***CXCL10*, *OAS1* and *MX1* are shown in Fig. 5A. Bottom: Immunoblot analyses confirming the corresponding knockdowns.**

(B) Expression of interferon-stimulated genes in SJSA-1 cells upon pharmacological inhibition of RNA Pol III. Cells were first treated with 70 μ M ML-60218 for 24 h, followed by transfection of 100 ng/mL poly(dA:dT) for 24 h. Graphs represent means of three independent replicates $\pm$ SEM.

(C) Expression of *IFIT1*, *IFIT2*, and *IFNB* in SJSA-1 cells after treatment with 1 μ M MI-1061 or 1 μ M MD-224 for 36 h, combined with transfection of 25 or 100 ng/mL poly(dA:dT) for the last 24 h. Graphs represent means of three independent replicates $\pm$ SEM. *CXCL10*, *OAS1* and *MX1* expression levels are displayed in Fig.5A.

(D) *Left*: Viability of SJSA-1 cells was determined by ATP-based luminescence (CellTiter-Glo) following siRNA-mediated knockdown of POLR3A or MDM2. Measurements were performed 48, 72, and 96 h post-transfection and normalized to the siRNA control indicating means of three independent replicates $\pm$ SEM. *Right*: Representative brightfield images of SJSA-1 cells acquired immediately prior to cell viability measurements. Scale bar: 100 μ m. **Bottom: Immunoblot analyses confirming the corresponding knockdown efficacies.**

(E) Expression of a panel of interferon-stimulated genes (ISGs) in MCF7 cells after POLR3A knockdown, or treatment with 1 μ M MI-1061 or 1 μ M MD-224 for 36 h, combined with poly(dA:dT) transfection, as described in (A). Graphs represent means of three independent replicates $\pm$ SEM. **Left: Immunoblot analysis verifying the corresponding POLR3A knockdown.**

(F) ISG expression in SJSA-1 cells after POLR3A knockdown, combined with transfection of 25 or 100 ng/mL poly(I:C). Shown are means of three independent replicates $\pm$ SEM.

(G) ISG expression in SJSA-1 cells after drug treatment as described in (A) and transfection of 25 or 100 ng/mL poly(I:C). Graphs represent means of three independent replicates $\pm$ SEM.

(H) Expression of *CXCL10*, *OAS1*, and *MX1* in SJSA-1 cells after STING knockdown and treatment as in (A) with 100 ng/mL poly(dA:dT) indicating means of three independent replicates $\pm$ SEM. **Right: Immunoblot analysis to confirm STING knockdown.**

(I) Expression of *CXCL10*, *OAS1*, and *MX1* in MCF7 cells after RIG-I or STING knockdown and treatment as in (A) with 100 ng/mL poly(dA:dT). Graphs represent means of three independent replicates $\pm$ SEM. **Right: Immunoblot analysis verifying the corresponding knockdowns.**

(J) Expression of *CXCL10* and *IFNB* in RPE cells after POLR3A knockdown and poly(dA:dT) transfection indicating means of three independent replicates $\pm$ SEM. **Bottom: Immunoblot analysis to confirm POLR3A knockdown.**

(K) Expression of *CXCL10*, *OAS1*, and *MX1* in RPE cells after RIG-I or STING knockdown and treatment as in (A) with 100 ng/mL poly(dA:dT). Graphs represent means of three independent replicates $\pm$ SEM. **Right: Immunoblot analysis confirming the corresponding knockdowns.**

(L) Expression of *CXCL10* and *IFNB* in MCF10A cells after POLR3A knockdown and poly(dA:dT) transfection. Graphs represent means of three independent replicates $\pm$ SEM. **Bottom: Immunoblot analysis to verify POLR3A knockdown.**

(M) Expression of *CXCL10*, *OAS1*, and *MX1* in MCF10A cells after RIG-I or STING knockdown and treatment as in (A) with 100 ng/mL poly(dA:dT). Graphs represent means of three independent replicates $\pm$ SEM. **Right: Immunoblot analysis confirming the corresponding knockdowns.**

(N) Immunoblot analyses of two independent SJSA-1 whole-cell lysates treated with 1 μ M MI-1061 or 1 μ M MD-224 for 36 h and transfected with 100 or 250 ng/mL poly(dA:dT) for the final 24 h; cf. Fig. 5B.

(O) Immunodetection of the ISG product MX1 in SJSA-1 cells treated with 1 μ M MI-1061 or 1 μ M MD-224 for 36 hours and transfected with 100 ng/mL poly(dA:dT) for the last 24 hours. Representative images reflect immunofluorescence staining of MX1 and MDM2, as well as DAPI staining. Scale bar: 50 μ m

(P) Expression of *IFIT1*, *IFIT2* and *IFNB* in SJSA-1 cells transfected with the RNA from pre-treated cells. SJSA-1 cells were treated with 1 μ M MI-1061 or 1 μ M MD-224 for 36 hours and transfected with 100 ng/mL poly(dA:dT) for the final 24 hours. RNA was extracted and transfected into freshly seeded SJSA-1 cells, which were then subjected to RNA extraction and RT-qPCR quantification of ISG expression. Graphs represent means of three independent replicates $\pm$ SEM; cf. Fig. 5D.

Statistical analyses: unpaired t-test; ns not significant; *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Suppl. Figure 6: MDM2 overexpression suppresses ISG expression and cell death in response to poly(dA:dT)

(A) H1299 cells were transfected with wild-type (wt) MDM2 or the MDM2 fragment 6–200. After 48 h, cells were transfected with 25 or 100 ng/mL poly(dA:dT) for 24 h. Expression of *IFIT1*,

IFIT2, and *IFNB* shows a reduced inflammatory response upon overexpression of either MDM2 construct. Graphs represent means of three independent replicates $\pm$ SEM. Expression levels of *CXCL10*, *OAS1* and *MX1* are shown in Fig. 6A.

(B) Immunoblot analyses of three independently prepared H1299 whole-cell lysates transfected with plasmids as in (A). After 48 h, the cells were transfected with 100 ng/mL poly(dA:dT) for 24 h. The quantification of the MX1 signals is shown in Fig. 6B.

(C) *Top*: Proliferation of H1299 cells from two independent experiments, measured by automated microscopy, following RIG-I knockdown and transfection with 1 μ g/mL poly(dA:dT). Data represent means of five technical replicates $\pm$ SEM. *Bottom*: Corresponding area-under-the-curve analysis, cf. Fig. 6C. **Right: Immunoblot analysis to confirm RIG-I knockdown.**

(D) *Top*: Proliferation of H1299 cells from two independent experiments upon overexpression of MDM2 and transfection with 1 μ g/mL poly(dA:dT). Means of three technical replicates $\pm$ SEM. *Bottom*: Area-under-the-curve analysis, cf. Fig. 6E.

(E) *Top*: Proliferation of SJSA-1 cells from three independent experiments, following RIG-I knockdown and transfection with 75 ng/mL poly(dA:dT). Means of three technical replicates $\pm$ SEM. *Bottom*: Area-under-the-curve analysis.

(F) Viability of SJSA-1 cells, 48 hours after transfection with 75 ng/mL poly(dA:dT), normalized to the siRNA control indicating means of three independent experiments $\pm$ SEM.

(G) Immunoblot analysis of independently obtained SJSA-1 cell lysates after RIG-I knockdown and transfection with 100 ng/mL poly(dA:dT) for 24 hours prior to harvest.

Statistical analyses: unpaired t-test; ns not significant; *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Suppl. Figure 7: MDM2 modulates the transcriptional response to NCS and represses inflammatory pathways

(A) Heat map depicting differentially expressed (DE) genes according to the z-score after performing DeSeq2 analysis on two different samples (DMSO or NCS, 1 μ g/mL for 72 hours) in SJSA-1 cells. Only genes with $|\log_2\text{fold}| \geq 0.8$ and adjusted p-value ($p_{\text{adj.}}$) < 0.05 were included in the analysis. Suppl. Table 3 displays DE genes and normalized reads.

(B) Gene set enrichment analysis (GSEA) of DMSO vs NCS; hallmarks (h.all.v2023.2).

(C) Upregulated genes upon treatment with NCS vs DMSO were correlated with the Kyoto Encyclopedia of Genes and Genomes (KEGG 2021 human) and the Molecular Signature

Database (MSigDB) Hallmark 2020 using the Enrichr platform to identify potentially perturbed pathways. Top 10 pathways, p-value ranked ($-\log_{10}$).

(D) Volcano plot showing $\log_2$ (fold change) vs $-\log_{10}$ (p-value) for all DE genes. Significantly regulated genes ($p < 0.05$ and $|\log_2\text{FC}| \geq 0.8$) are highlighted in blue (downregulated) and red (upregulated). Comparison: SJSA-1 cells treated with NCS vs DMSO.

(E) Heat map, as in (A), showing gene expression changes in cells pre-treated with DMSO or NCS for 72 hours, followed by treatment with DMSO, 1 μM MI-1061, or 1 μM MD-224 for the final 24 hours. Suppl. Table 6 contains all DE genes and normalized reads. See Fig. 7A-F for a more comprehensive analysis of NCS-treated samples.

(F) Downregulated genes in NCS + MI-1061 samples compared to the others were correlated with the Molecular Signature Database (MSigDB) Hallmark 2020 using the Enrichr platform to identify potentially impaired pathways. Top 10 pathways, p-value ranked ($-\log_{10}$). Cf. Fig. 7A-E.

Suppl. Figure 8: MDM2 attenuates the inflammatory response following DNA double-strand breaks

(A) Expression of *IFIT1*, *IFIT2*, and *IFNB* in SJSA-1 cells after RIG-I, IRF3, or POLR3A knockdown and treatment with 1 $\mu\text{g/mL}$ NCS for 48 hours, followed by refreshed NCS treatment for 24 h. Graphs represent means of three independent replicates $\pm$ SEM. *CXCL10*, *OAS1* and *MX1* expression levels are displayed in Fig.8A.

(B) Expression of interferon-stimulated genes in SJSA-1 cells treated with an RNA Pol III inhibitor. Cells were first treated with 70 μM ML-60218 for 24 h, followed by treatment with 1 $\mu\text{g/mL}$ NCS for 48 h. Subsequently, cells received fresh medium containing NCS and ML-60218 for an additional 24 h. Graphs indicate means of three independent replicates $\pm$ SEM.

(C) Expression of *IFIT1*, *IFIT2*, and *IFNB* in SJSA-1 cells after treatment with 1 $\mu\text{g/mL}$ NCS for 48 hours, followed by refreshed NCS treatment for 24 h. 1 μM MI-1061 or 1 μM MD-224 was added during the second treatment. Graphs represent means of three independent replicates $\pm$ SEM. *CXCL10*, *OAS1* and *MX1* expression levels are displayed in Fig.8A.

(D) Expression of *IFIT1*, *IFIT2*, and *IFNB* in SJSA-1 cells following POLR3A knockdown and γ -irradiation (5 Gy or 10 Gy) 72 hours prior to harvest. Cells were treated with 1 μM MI-1061 or 1 μM MD-224 during the last 24 hours. Graphs represent means of three independent replicates $\pm$ SEM. Expression levels of *CXCL10*, *OAS1* and *MX1* are shown in Fig.8B.

(E) Expression of a panel of interferon-stimulated genes in MCF7 cells after treatment with 1 $\mu\text{g/mL}$ NCS for 48 h, followed by refreshed NCS treatment for 24 h. 1 μM MI-1061 or 1 μM

MD-224 was added during the refreshed treatment. Graphs indicate means of three independent replicates $\pm$ SEM.

Statistical analyses: unpaired t-test; ns not significant; *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Suppl. Figure 9: MDM2 limits the inflammatory response and protects cells from DNA damage-induced growth arrest

(A) Expression of *IFIT1*, *IFIT2*, and *IFNB* in H1299 cells transfected to express MDM2. Cells were treated with 1 $\mu\text{g/mL}$ NCS at 24 hours and 72 hours post-transfection and harvested 96 hours after transfection. Graphs represent means of three independent replicates $\pm$ SEM. Corresponding analyses of *CXCL10*, *OAS1* and *MX1* are shown in Fig.9A.

(B) Proliferation of H1299 cells following RIG-I knockdown and treatment with 0.75 $\mu\text{g/mL}$ NCS on days 1 and 3, measured by automated microscopy in three independent replicates, cf. Fig. 9B.

(C) Representative images of crystal violet-stained cells at the endpoint of the proliferation assay shown in (B). Quantification of crystal violet absorbance shown in Fig. 9C.

(D) Proliferation of H1299 cells overexpressing MDM2 and treated with 0.75 $\mu\text{g/mL}$ NCS on days 1 and 3; three independent replicates, cf. Fig. 9D.

(E) Representative images of crystal violet-stained cells at the endpoint of the proliferation assay shown in (D). Quantification of crystal violet absorbance displayed in Fig. 9E.

(F) Brightfield images of H1299 cells overexpressing MDM2 and treated with 0.75 $\mu\text{g/mL}$ NCS on days 1 and 3. Scale bar: 100 μm .

(G) Proliferation of SJSA-1 cells following RIG-I knockdown and treatment with 1 $\mu\text{g/mL}$ NCS on days 1 and 3; five independent replicates. *Top right*: corresponding area-under-the-curve analysis indicating means of four independent experiments $\pm$ SEM.

(H) *Top*: Representative images of crystal violet-stained cells at the endpoint of the proliferation assay shown in (G). *Bottom*: Quantification of crystal violet absorbance indicating means of four independent experiments $\pm$ SEM.

(I) Brightfield images of SJSA-1 cells at day 5 after RIG-I knockdown and treatment with 1 $\mu\text{g/mL}$ NCS on days 1 and 3. Scale bar: 100 μm .

Statistical analyses: unpaired t-test; ns not significant; *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

SUPPLEMENTAL TABLES

Suppl. Table 1: Differential gene expression analysis by deep sequencing of small RNAs, performed with DESeq2, in SJSA-1 cells treated with MI-1061 (Mi; 1 μ M), MD-224 (MD; 1 μ M) or Nutlin (20 μ M) for 12 h in triplicates or duplicates. Log2 fold changes (log2FC), p-values, and adjusted p-values are shown. Genes were filtered to meet adjusted p-value (padj) < 0.05 and $|\log_2FC| \geq 0.1$. Normalization was performed using mitochondrial tRNA and the normalized counts are provided for each sample.

Suppl. Table 2: Mass-spectrometry – protein candidates identified in SJSA-1 cells treated with DMSO or 20 μ M Nutlin and transfected or not with 100 ng/mL poly(dA:dT) (Poly). Proteins were filtered to meet p-value < 0.05 and $|\log_2FC| \geq 0.8$.

Suppl. Table 3: Mass-spectrometry – protein candidates identified in H1299 cells transfected with a control vector (C) or with expression plasmids for MDM2 wt (M) or mutant 6-200 (MM), and then transfected or not with 100 ng/mL poly(dA:dT) (P). Proteins were filtered to meet p-value < 0.05 and $|\log_2FC| \geq 0.8$.

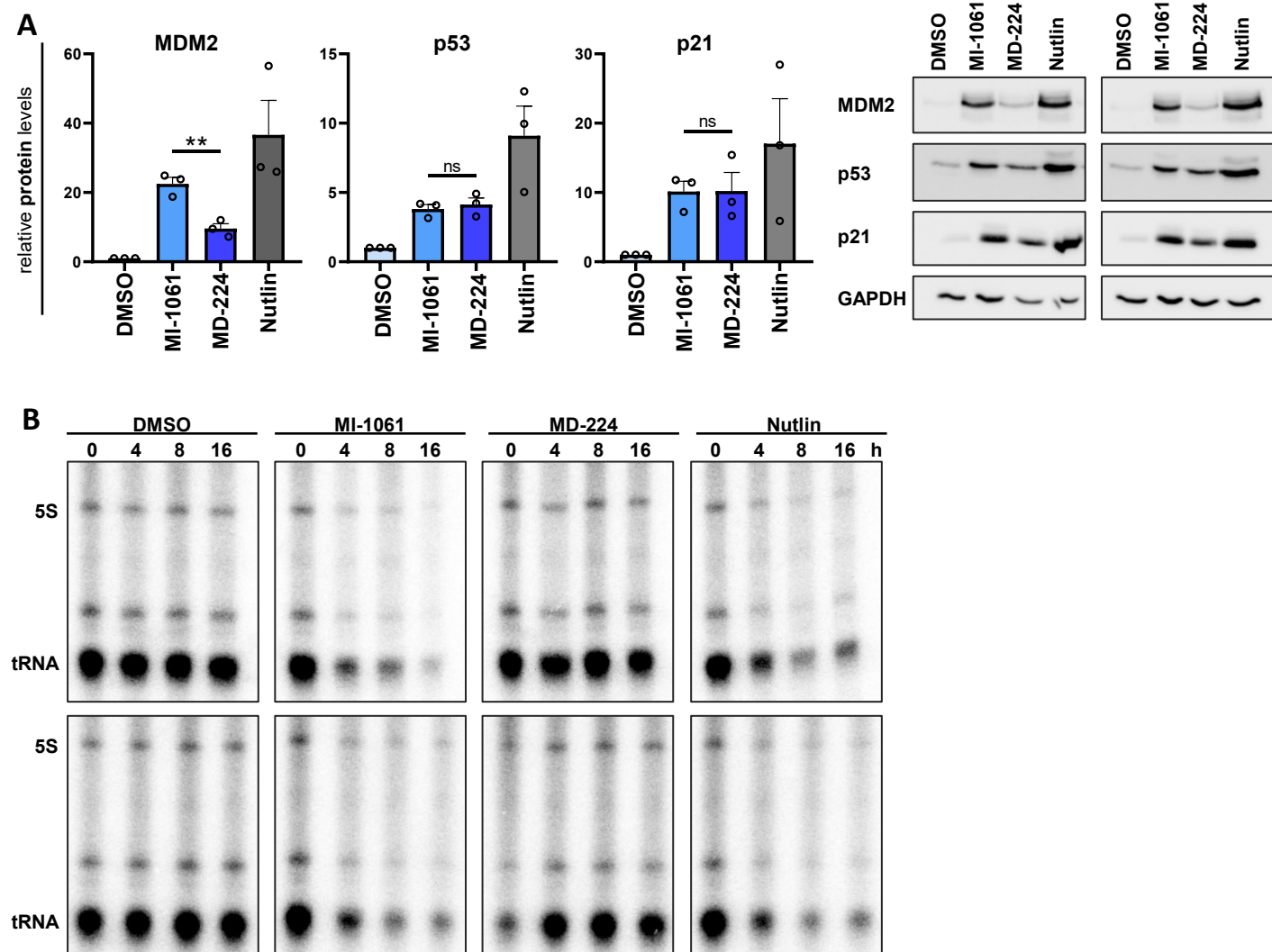
Suppl. Table 4: Differential gene expression analysis of RNA-sequencing data, performed with DESeq2, in SJSA-1 cells treated with NCS (N; 1 μ g/mL for 72 h) and either DMSO (D), MI-1061 (Mi; 1 μ M), or MD-224 (Md; 1 μ M). Log2 fold changes (log2FC), p-values, and adjusted p-values are shown for pairwise comparisons of MI-1061 and MD-224 relative to the control condition DMSO in the presence of NCS. Genes were filtered to meet adjusted p-value (padj) < 0.05 and $|\log_2FC| \geq 0.8$. The analysis was based on raw read counts and a negative binomial model, and normalized counts are provided for each sample in triplicates.

Suppl. Table 5: Differential gene expression analysis of RNA-sequencing data, performed with DESeq2 as in Suppl. Table 2, in SJSA-1 cells treated with DMSO (D; control) or NCS (N; 1 μ g/mL for 72 h). Log2 fold changes (log2FC), p-values, and adjusted p-values are shown for the comparison of NCS-treated cells relative to DMSO. Genes were filtered to meet adjusted p-value (padj) < 0.05 and $|\log_2FC| \geq 0.8$.

Suppl. Table 6: Differential gene expression analysis of RNA-sequencing data from SJSA-1 cells was performed using DESeq2 as in Suppl. Table 2. Cells were pretreated with either DMSO (D; control) or NCS (N; 1 μ g/mL for 72 h), followed by treatment with DMSO, MI-1061

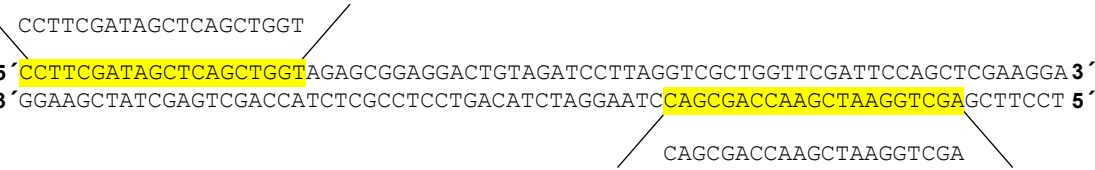
(Mi; 1 μ M), or MD-224 (Md; 1 μ M) for the final 24 h. Separate tables of log₂ fold changes (log₂FC), p-values, and adjusted p-values are provided for each pretreatment condition (DMSO or NCS), showing pairwise comparisons of MI-1061 and MD-224 relative to DMSO. Genes included in the tables were filtered to meet padj < 0.05 and |log₂FC| $\geq$ 0.8 based on the NCS-pretreated samples.

Suppl. Figure 1

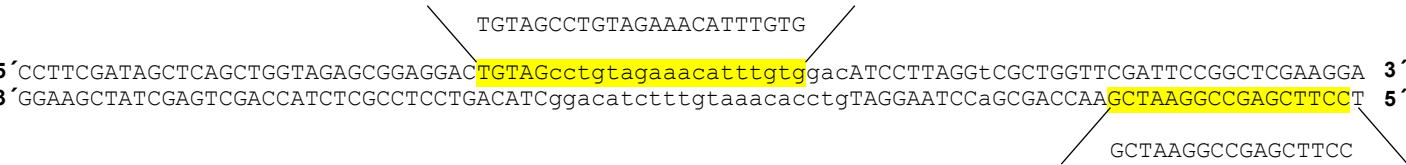


C

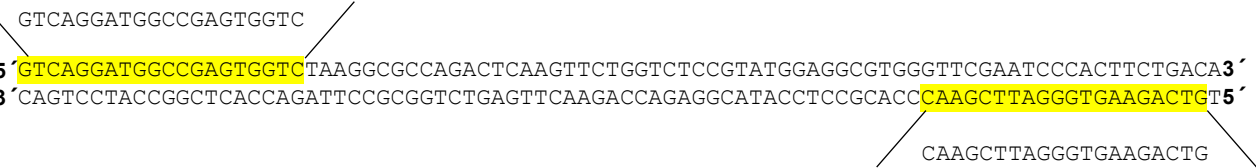
total tRNA-Tyr-GTA-4-1 primer binding



pre-tRNA-Tyr-GTA-5-3 primer binding

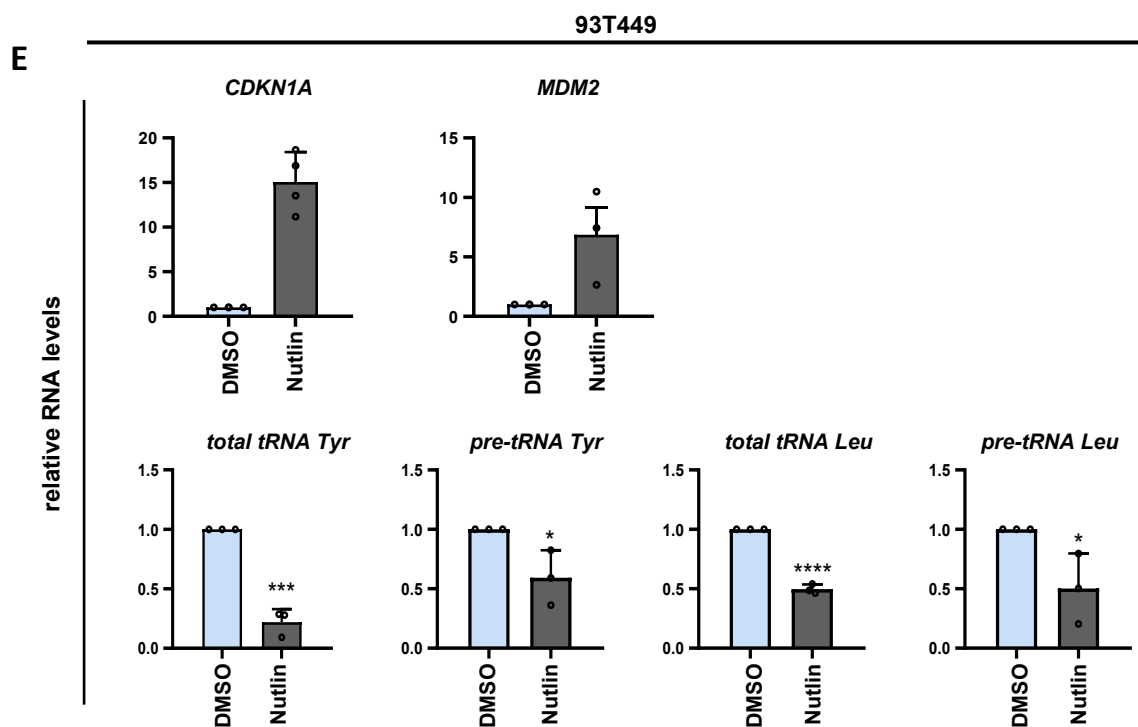
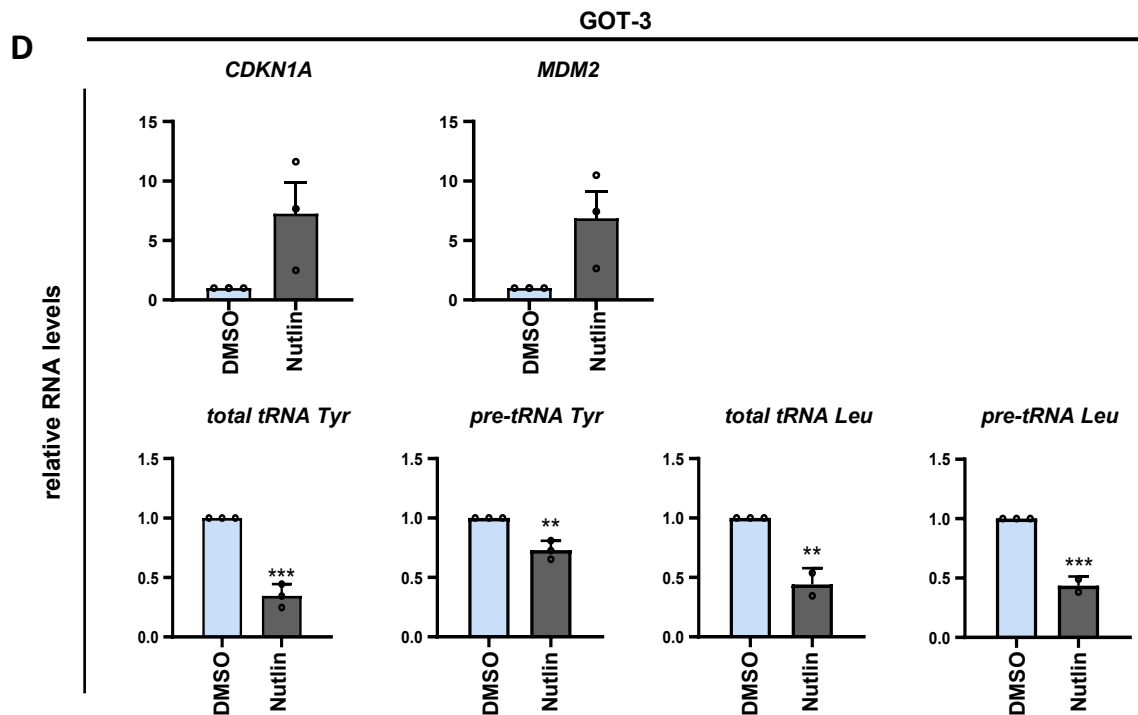


total tRNA-Leu-CAA-2-1 primer binding

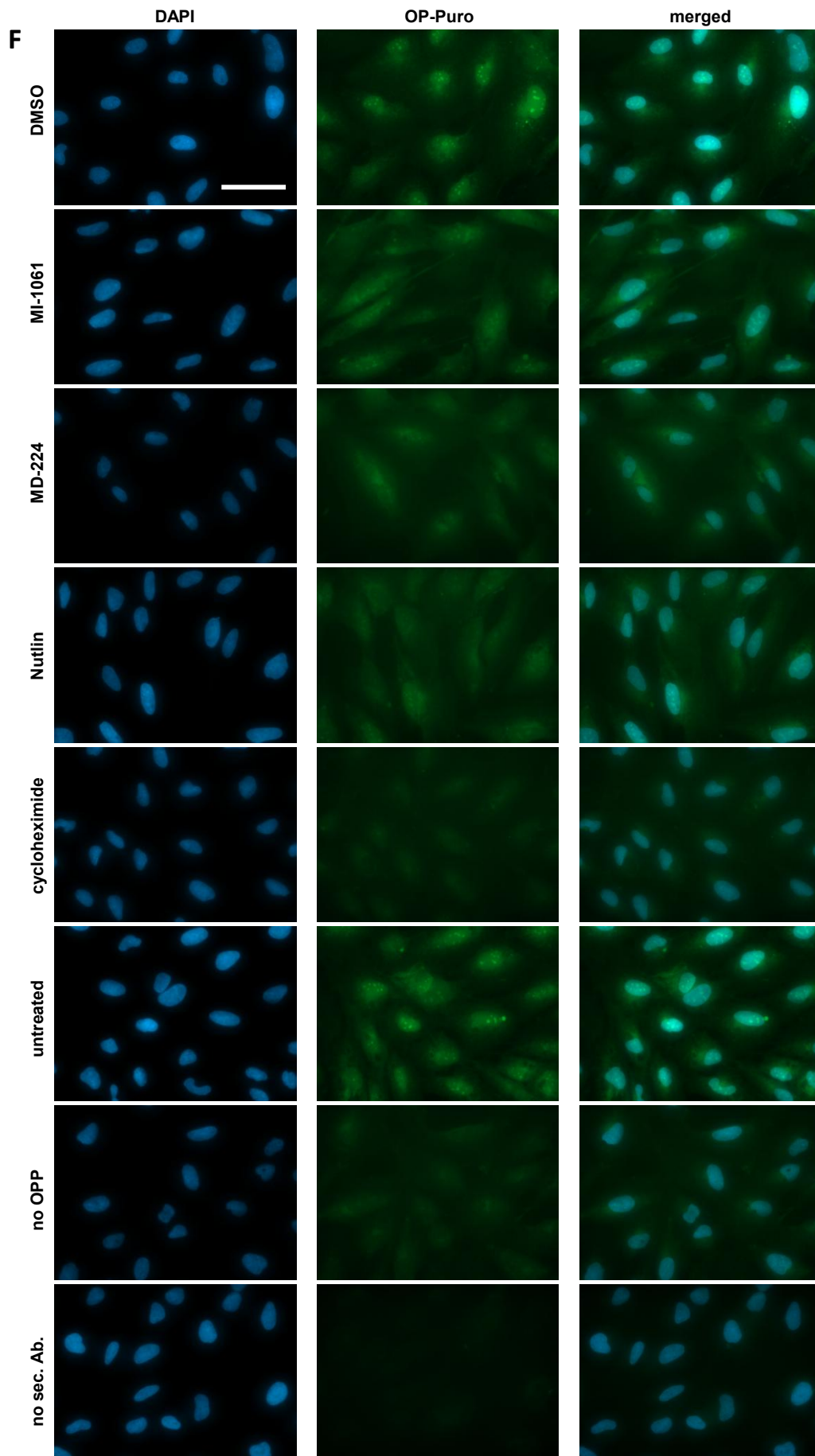


pre- tRNA-Leu-CAA-4-1 primer binding

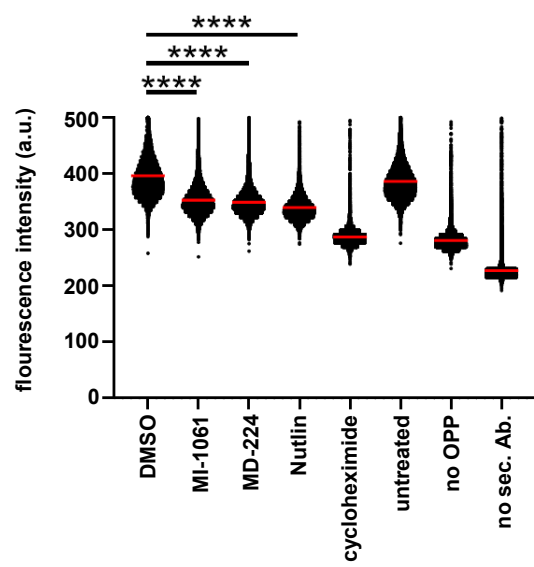




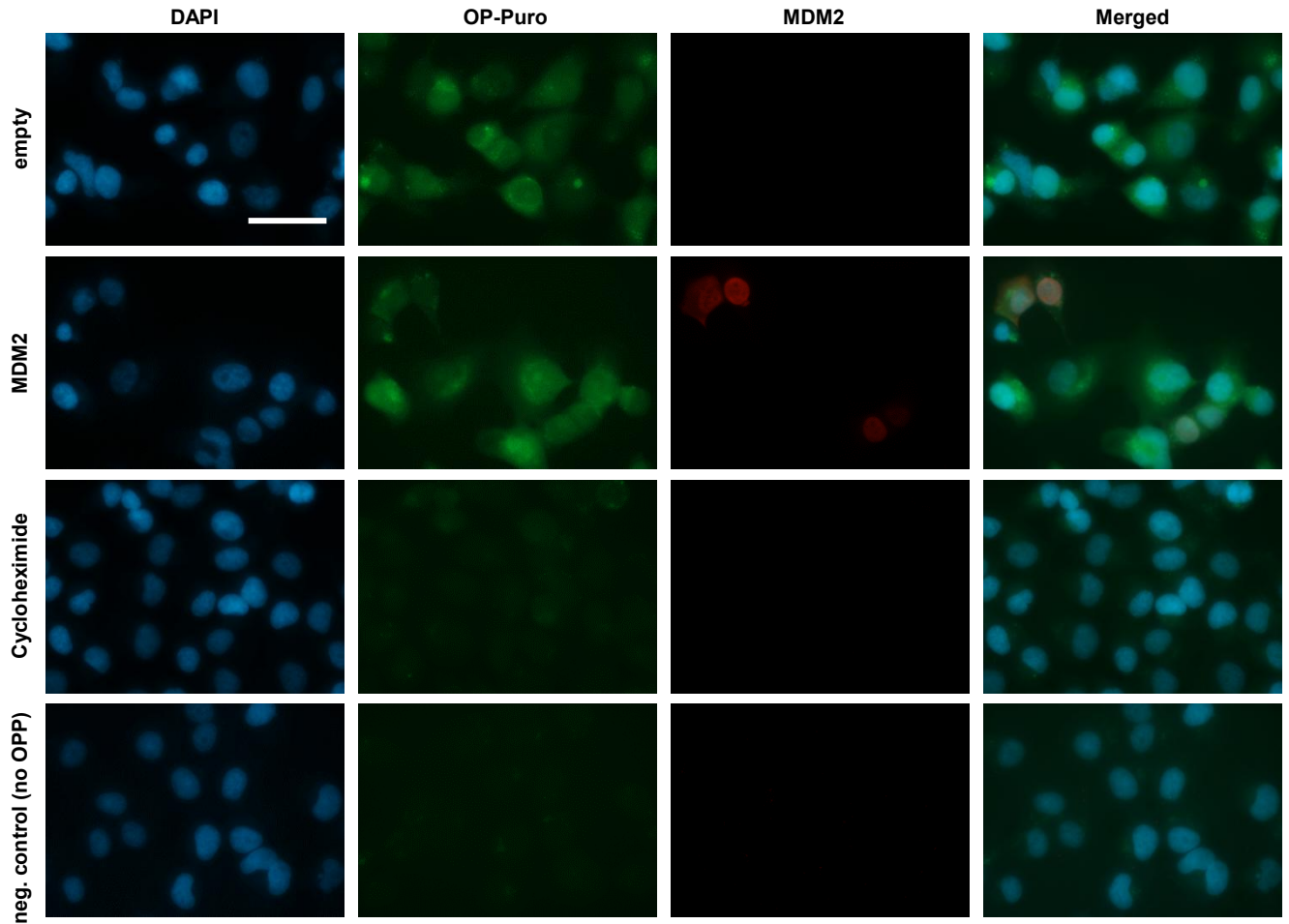
Suppl. Figure 1, continued



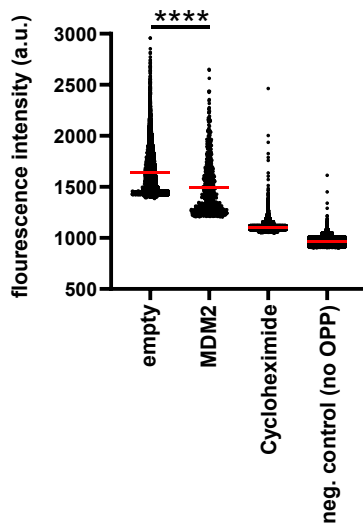
G



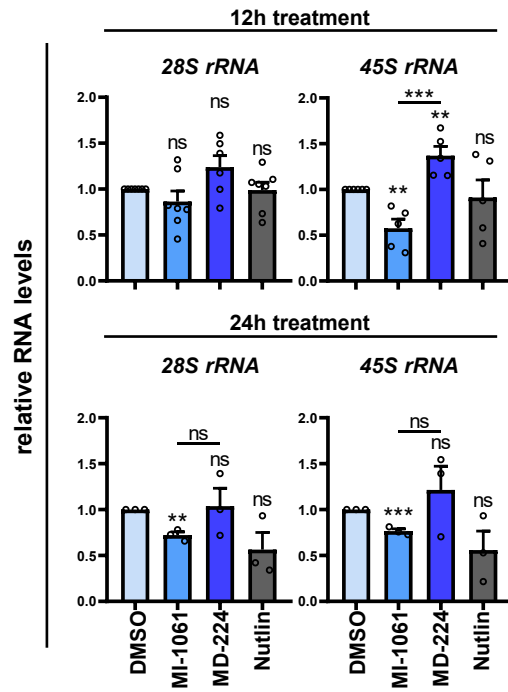
H



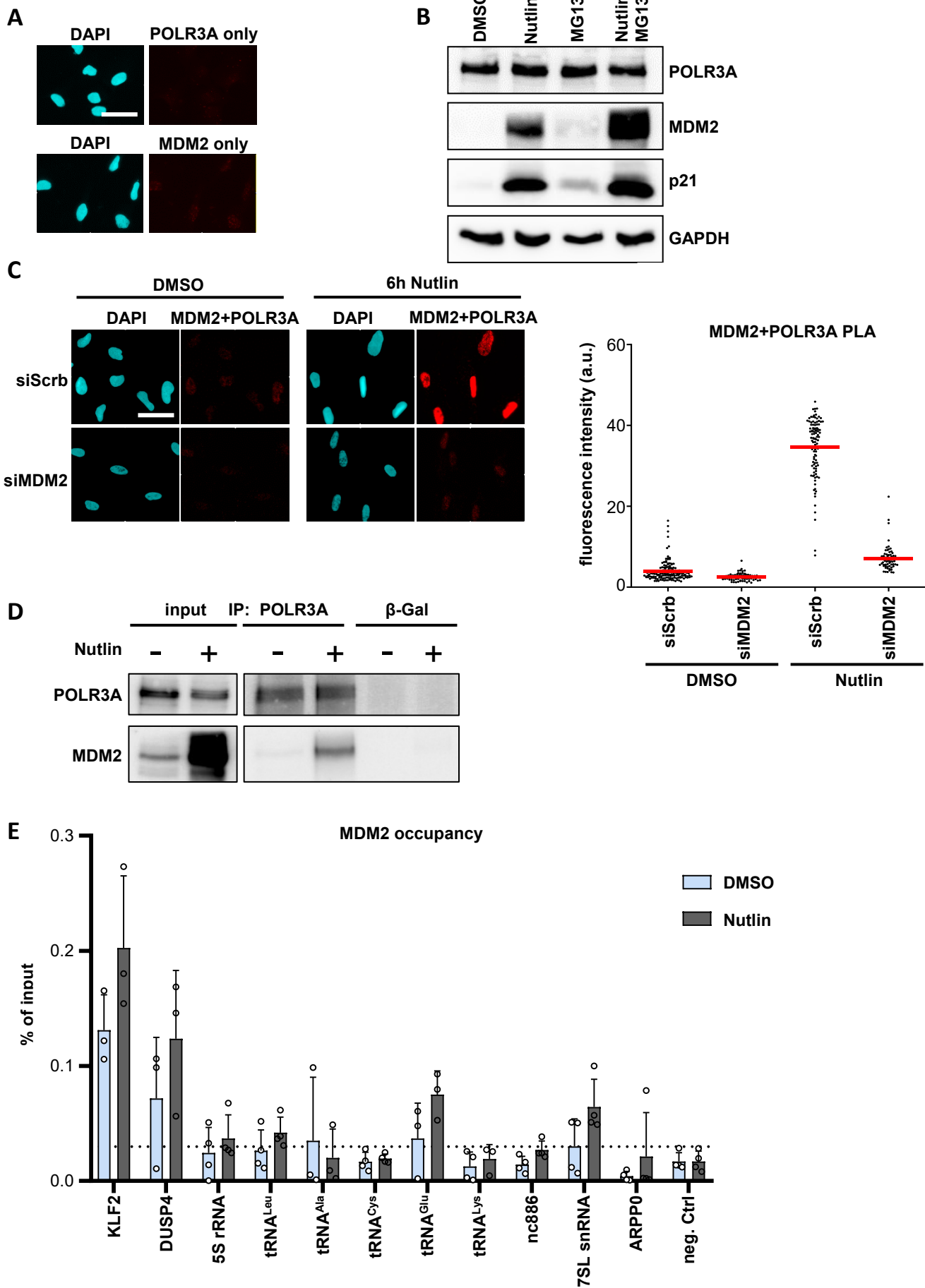
I



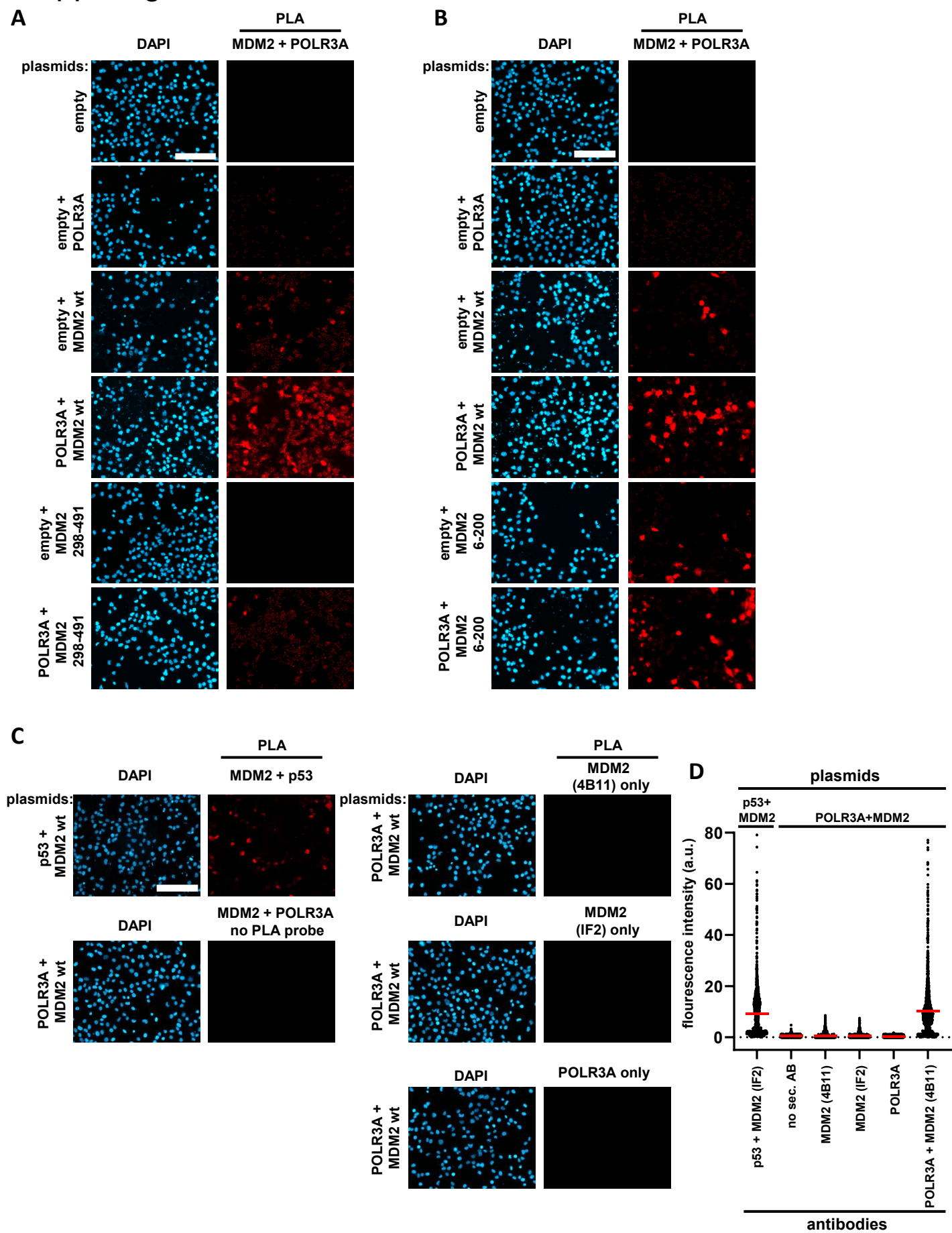
J



Suppl. Figure 2

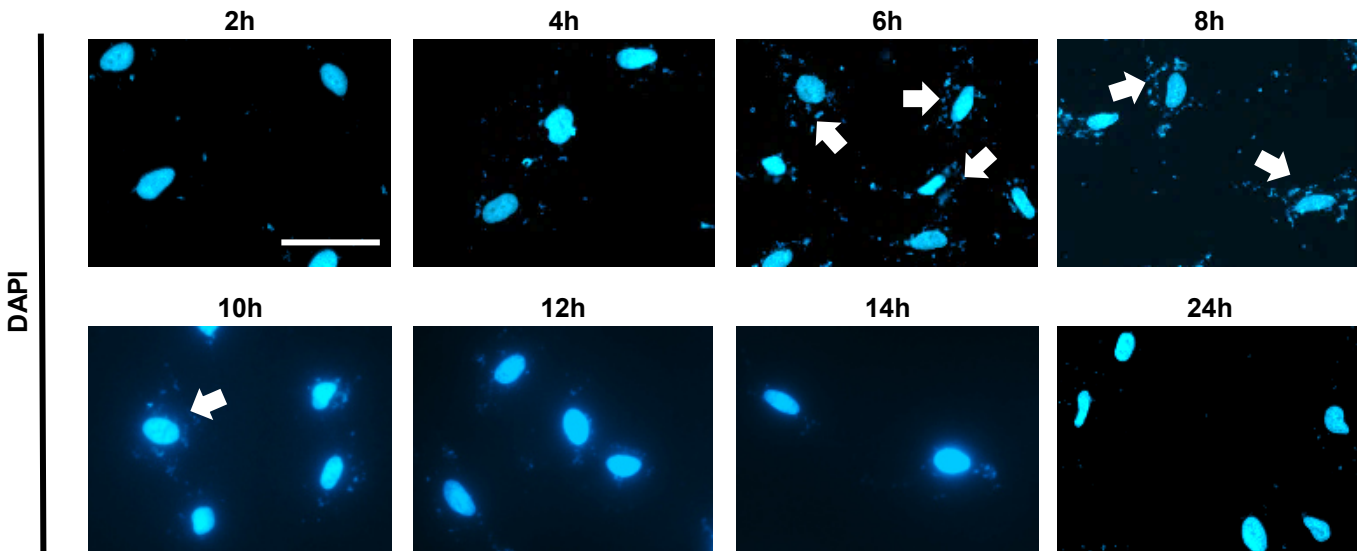


Suppl. Figure 3

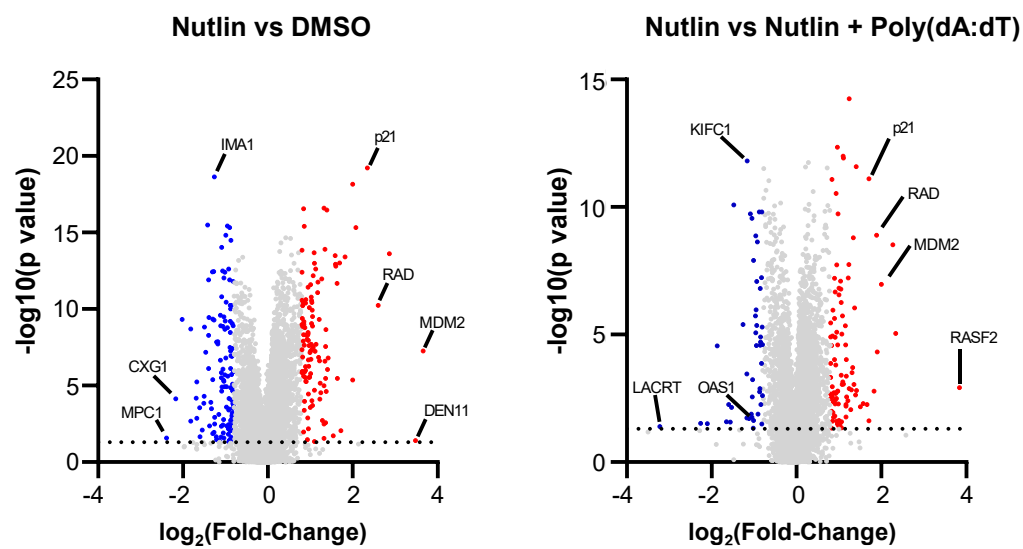


Suppl. Figure 4

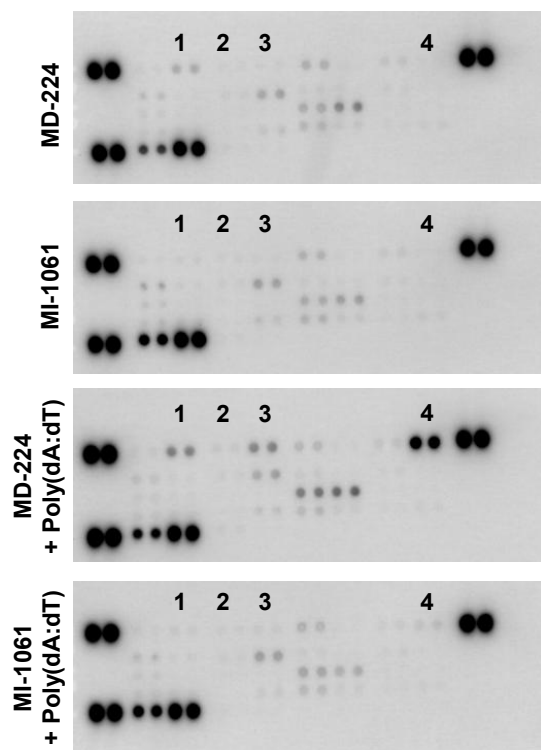
A



B

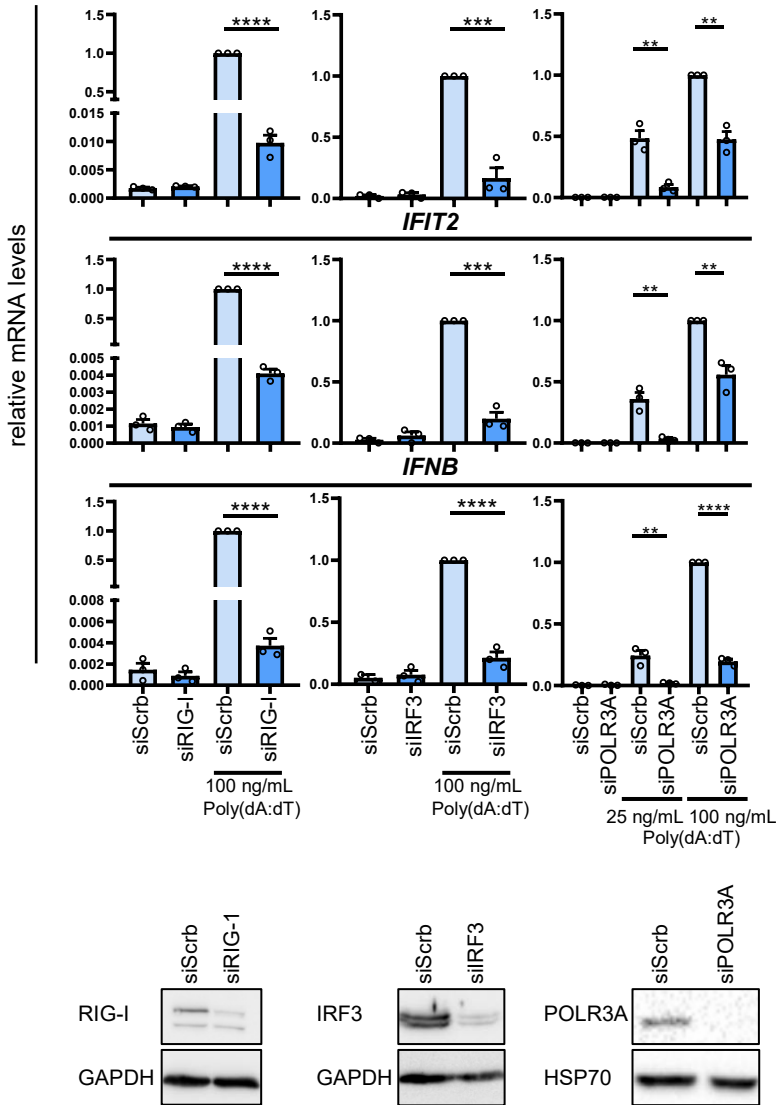


c

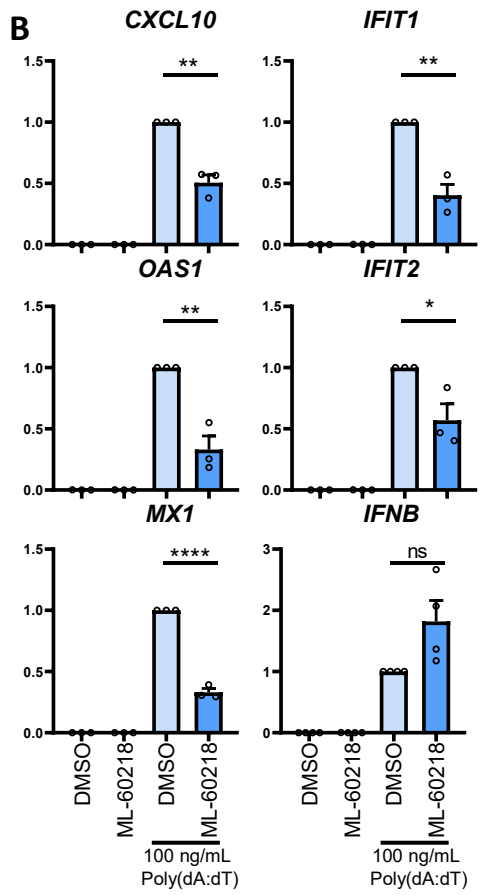


SJSA-1

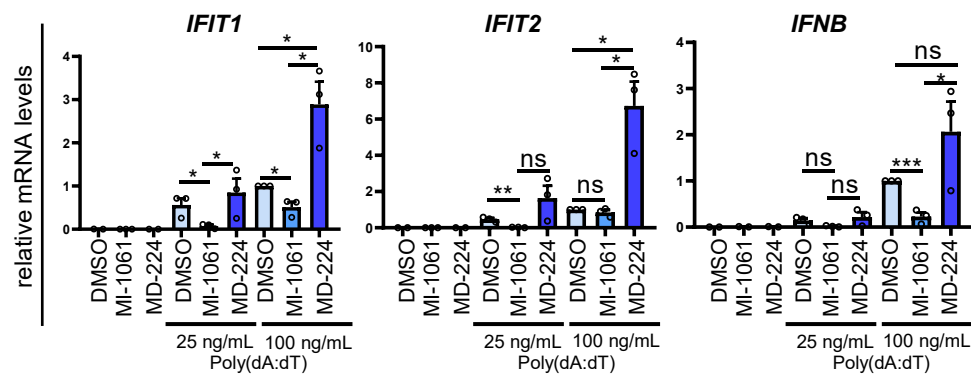
A



B

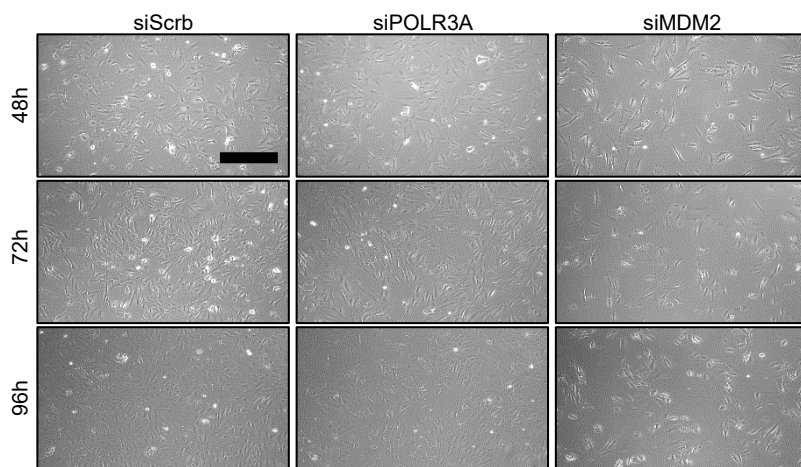
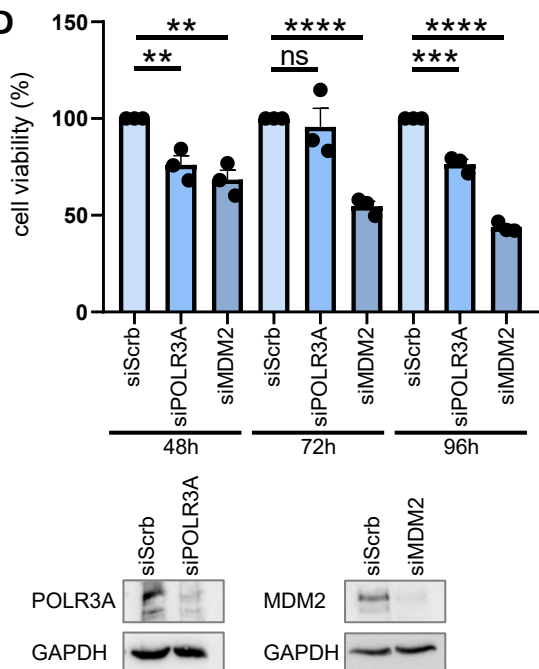


C



Suppl. Figure 5, continued

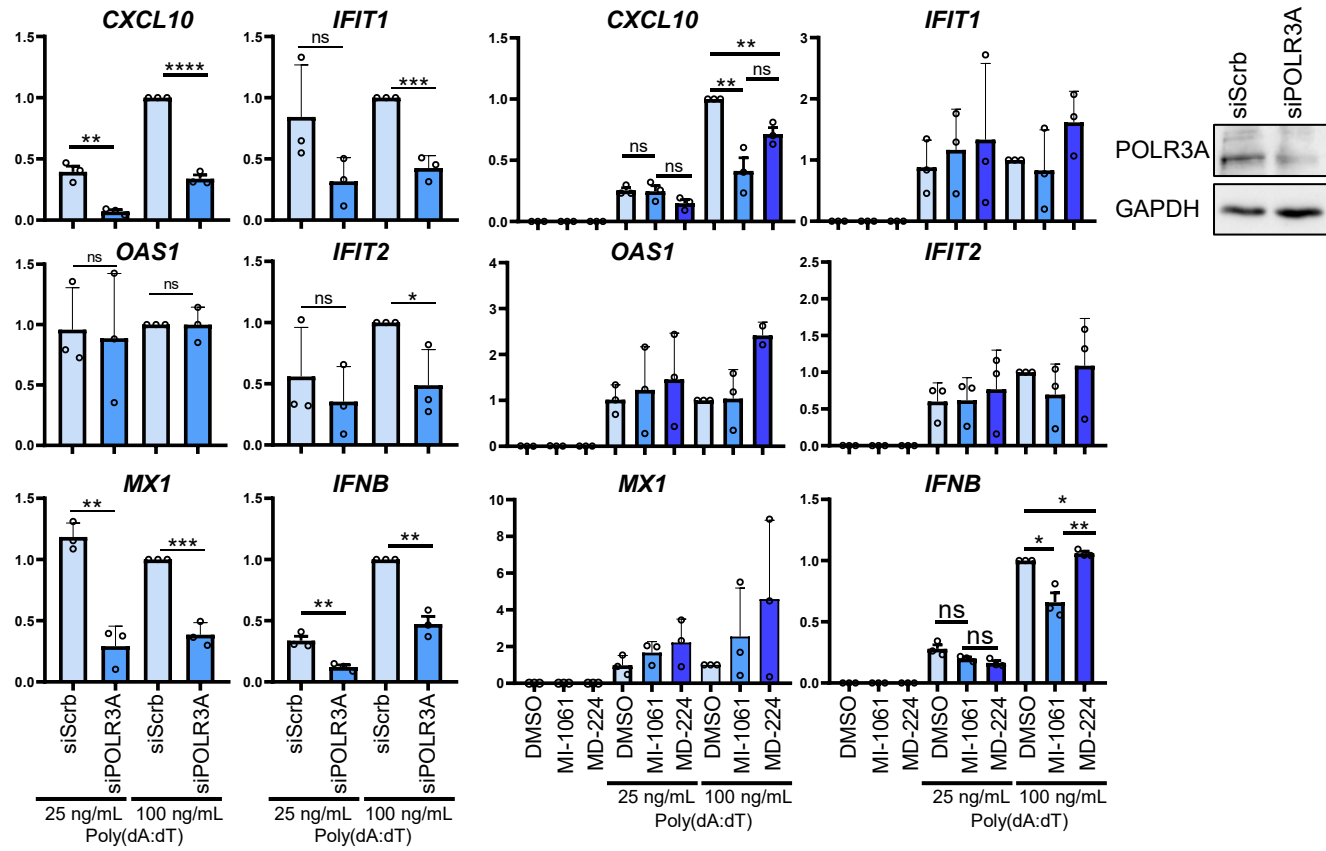
D



MCF7

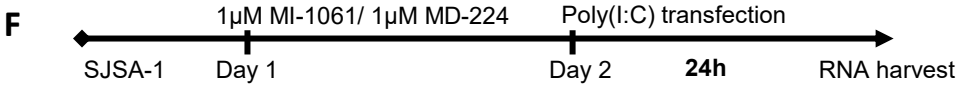
E

relative mRNA levels

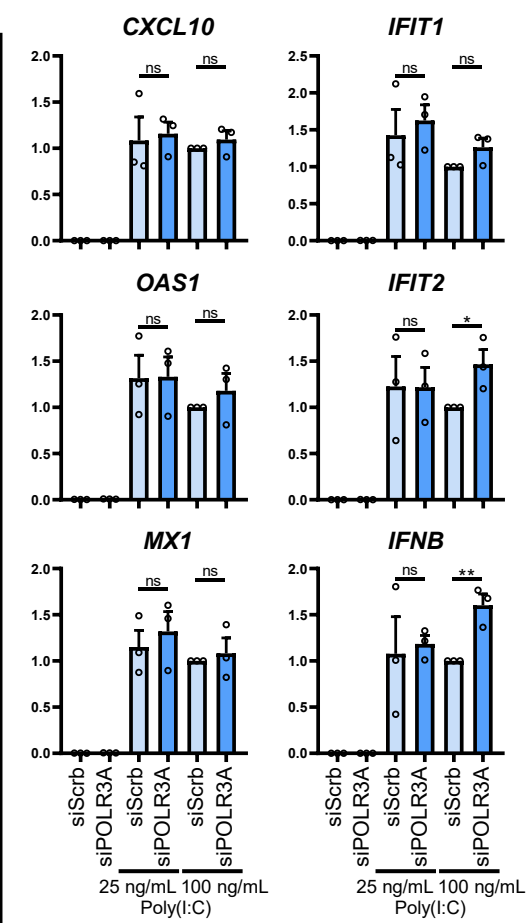


Suppl. Figure 5, continued

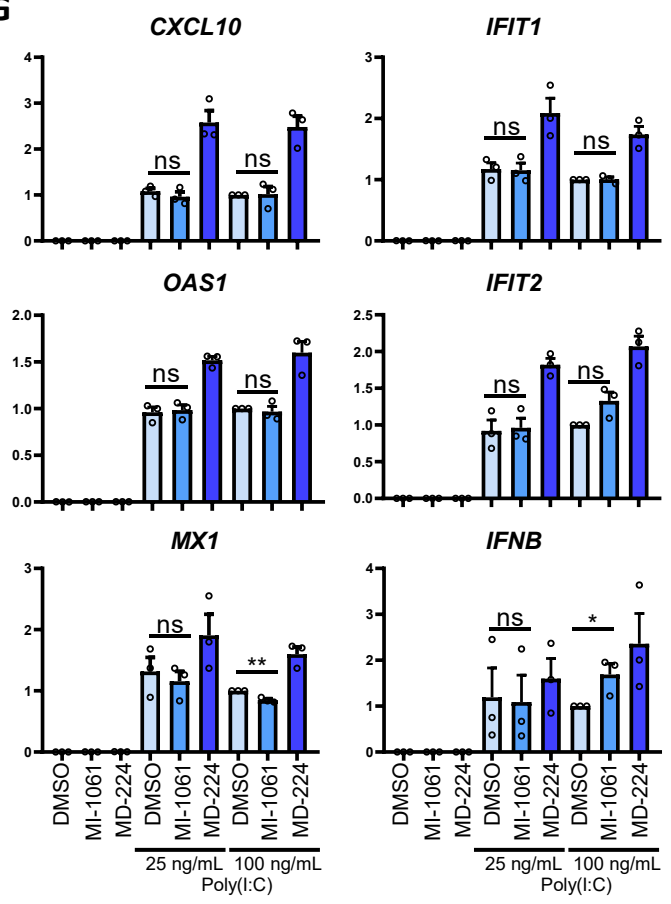
F



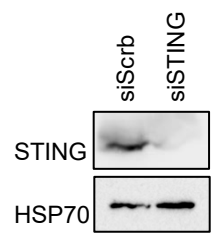
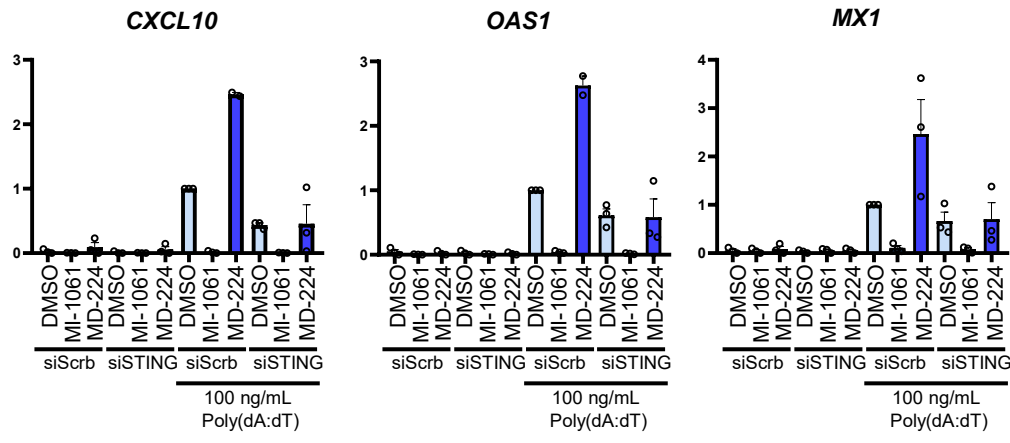
relative mRNA levels



G

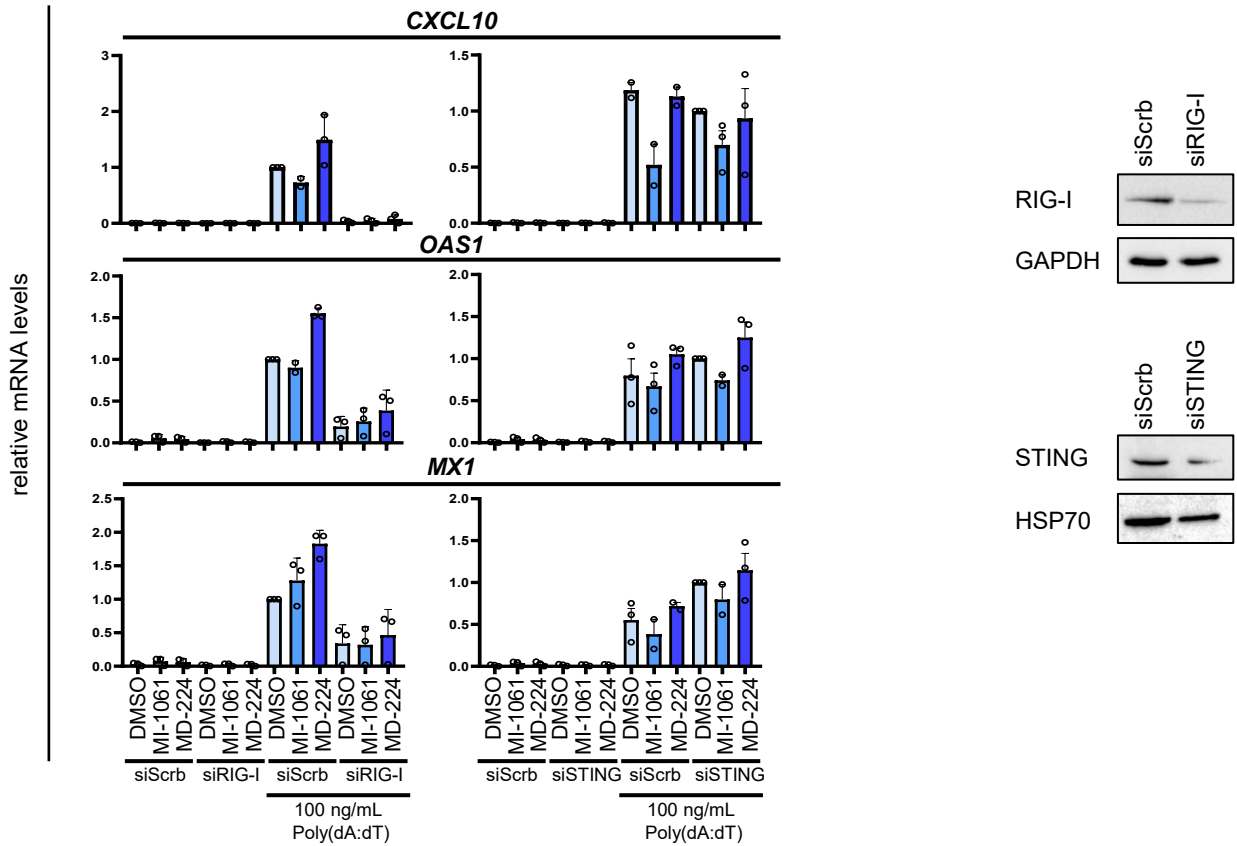


H



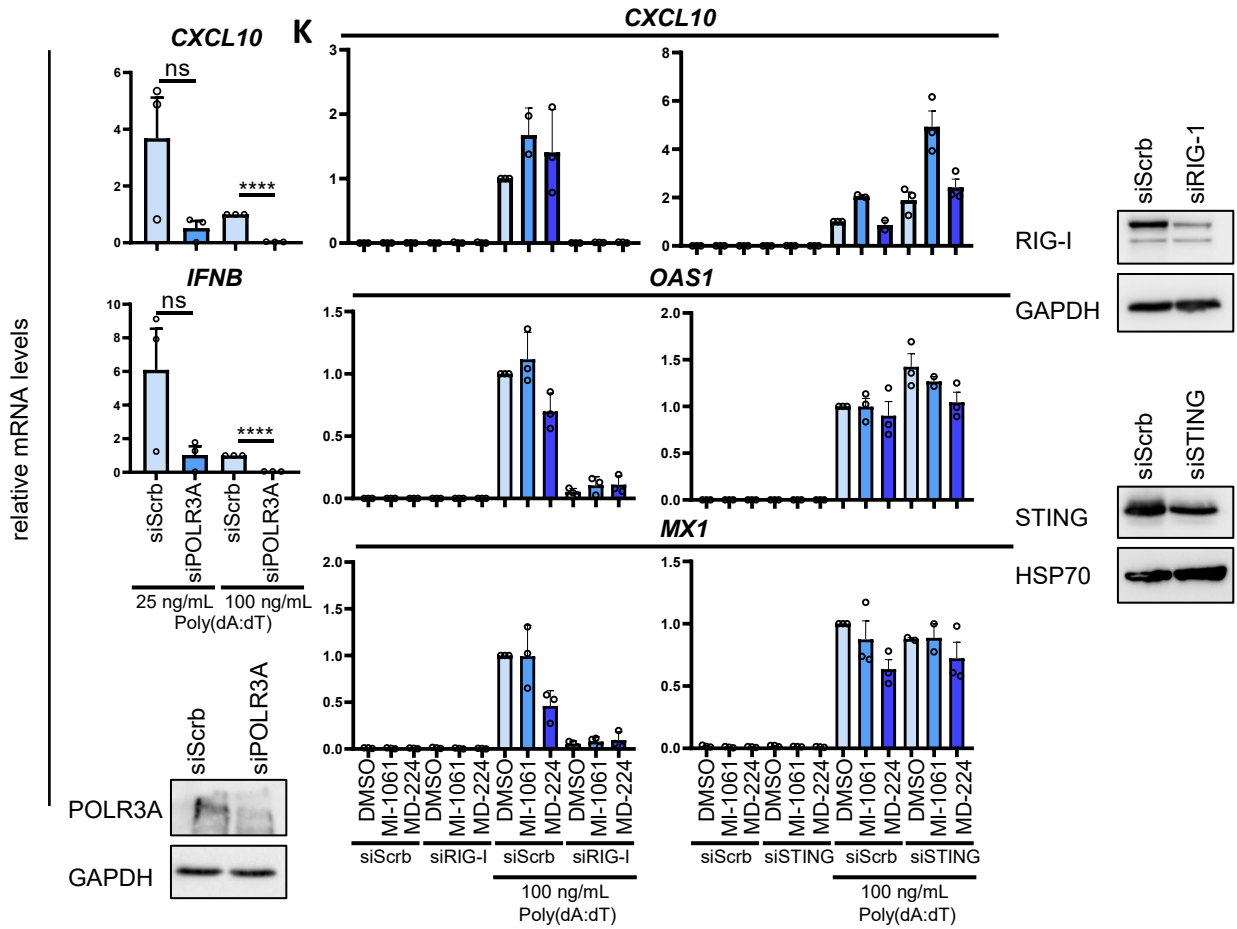
MCF7

I



RPE

J



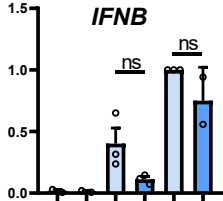
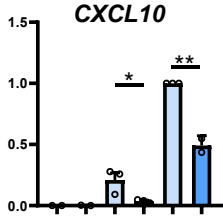
MCF10A

L

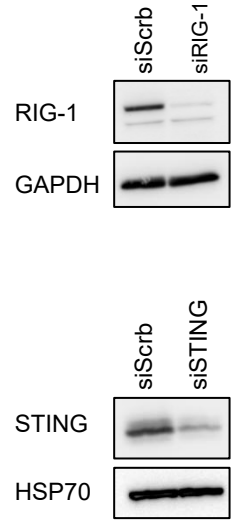
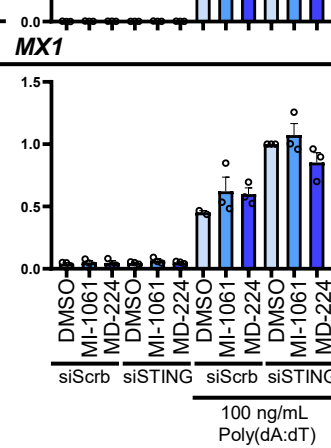
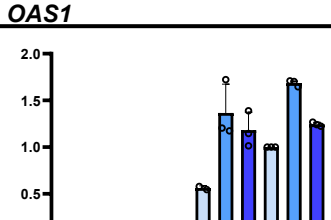
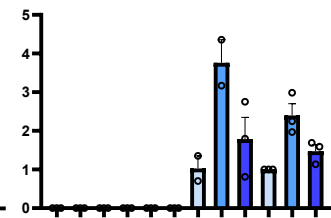
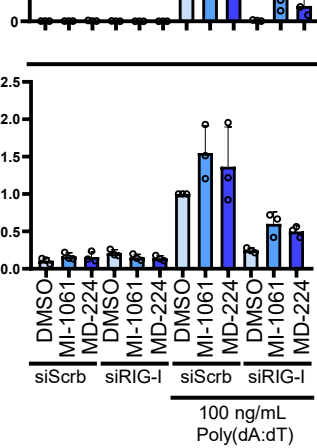
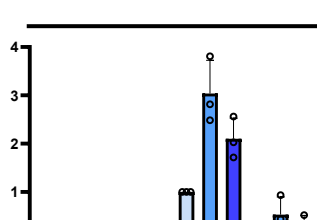
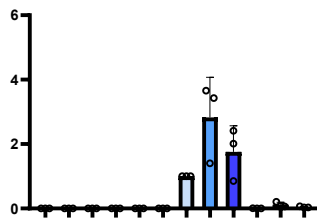
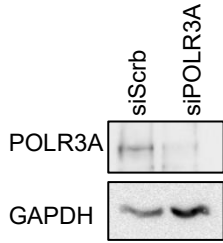
relative mRNA levels

M

CXCL10

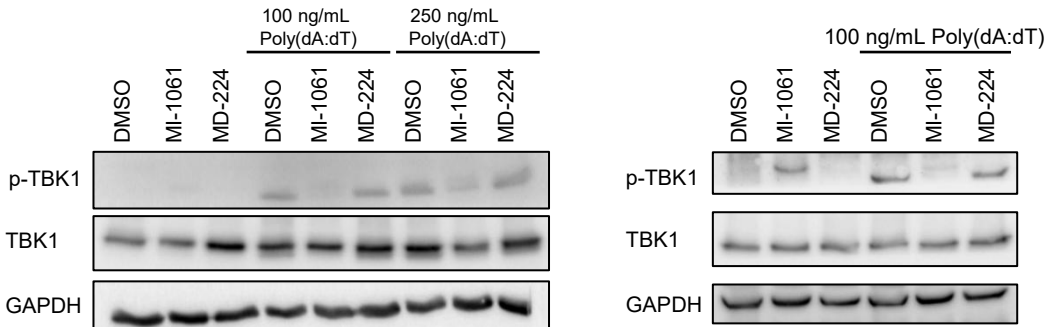


25 ng/mL 100 ng/mL
Poly(dA:dT)

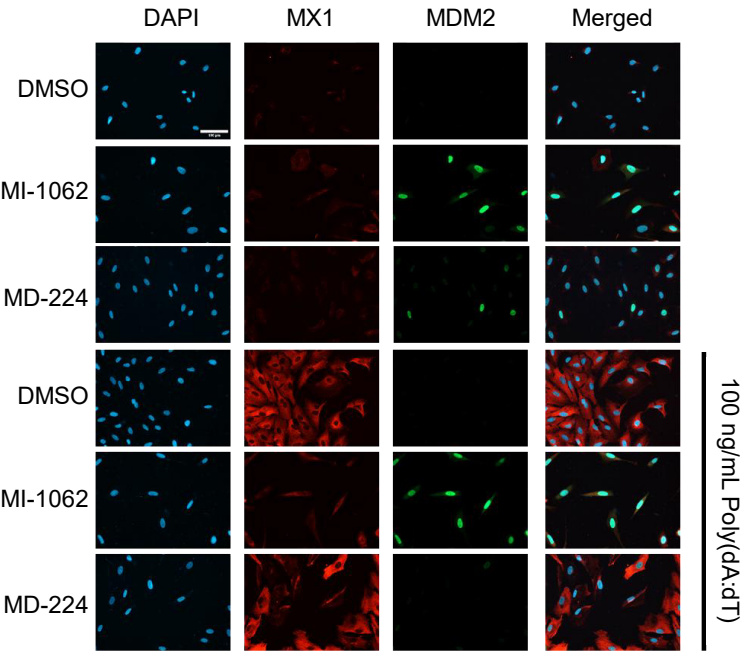


SJSA-1

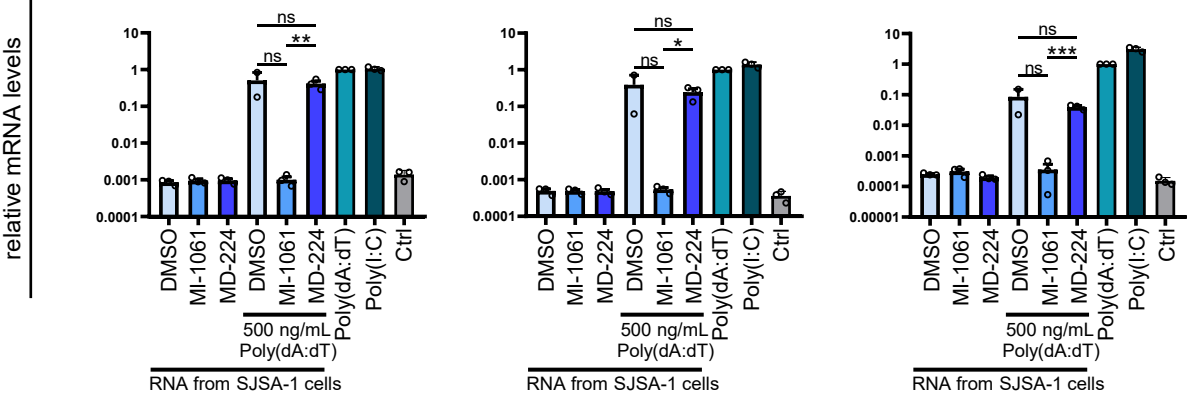
N

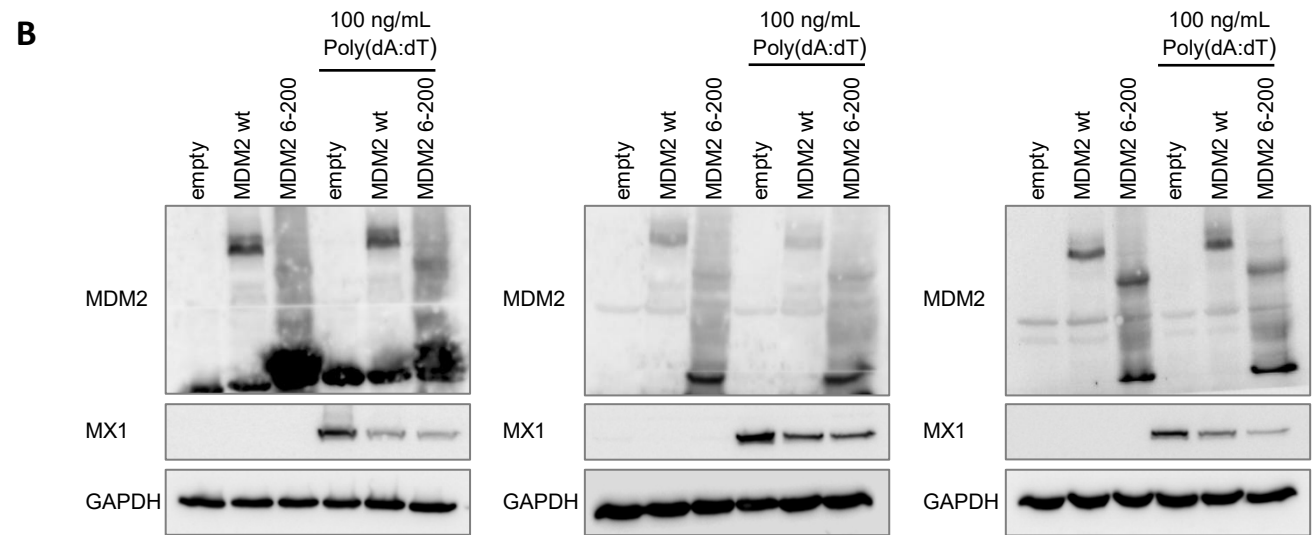
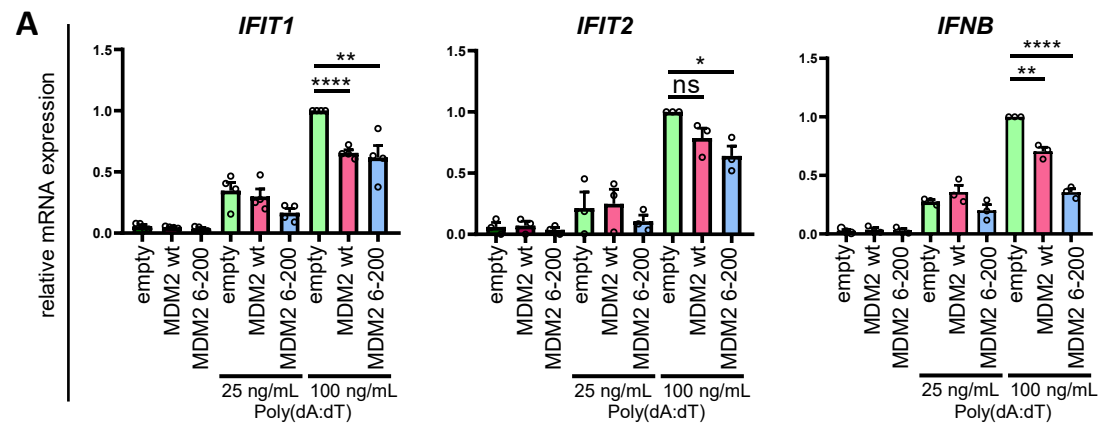


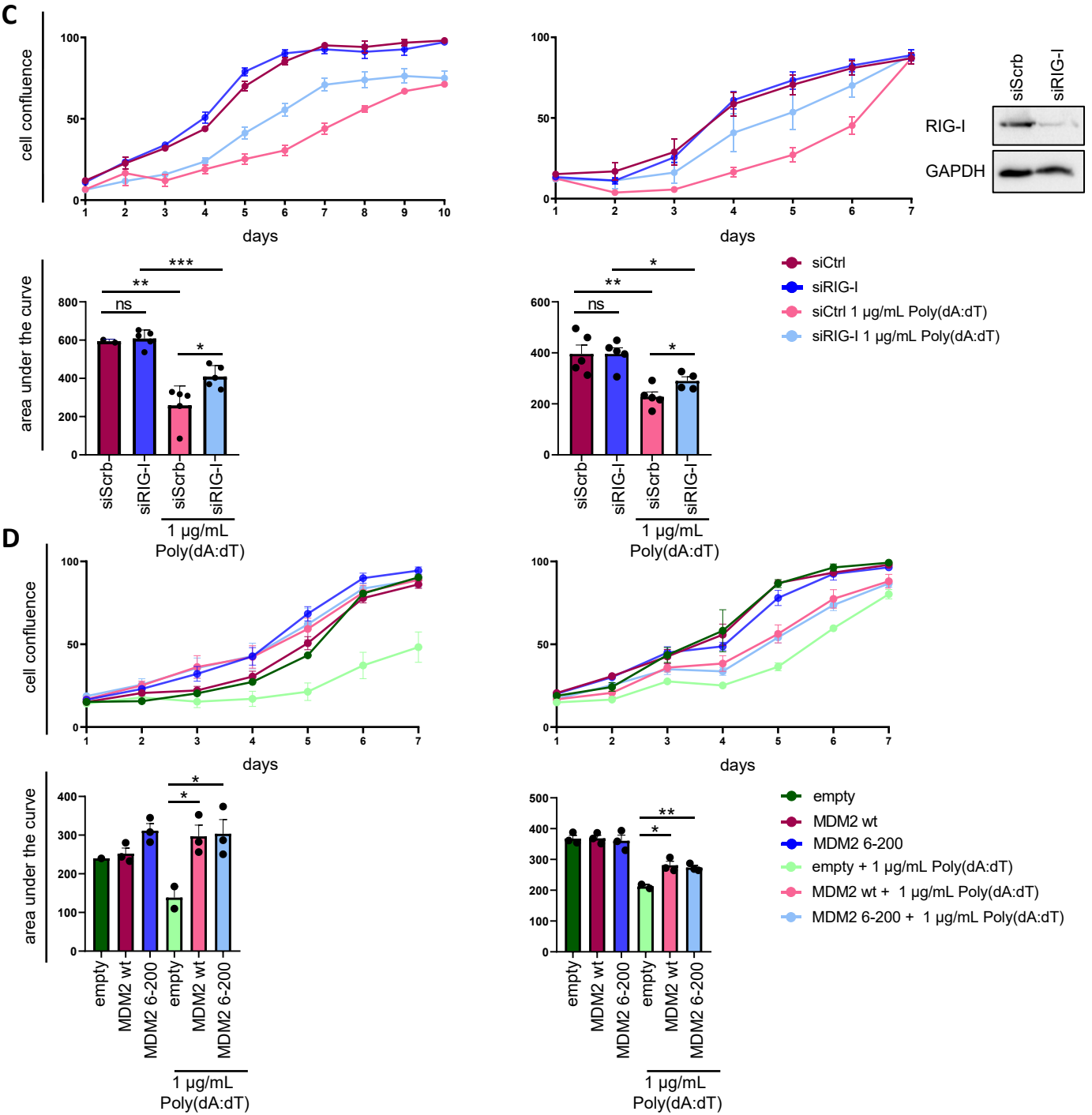
O



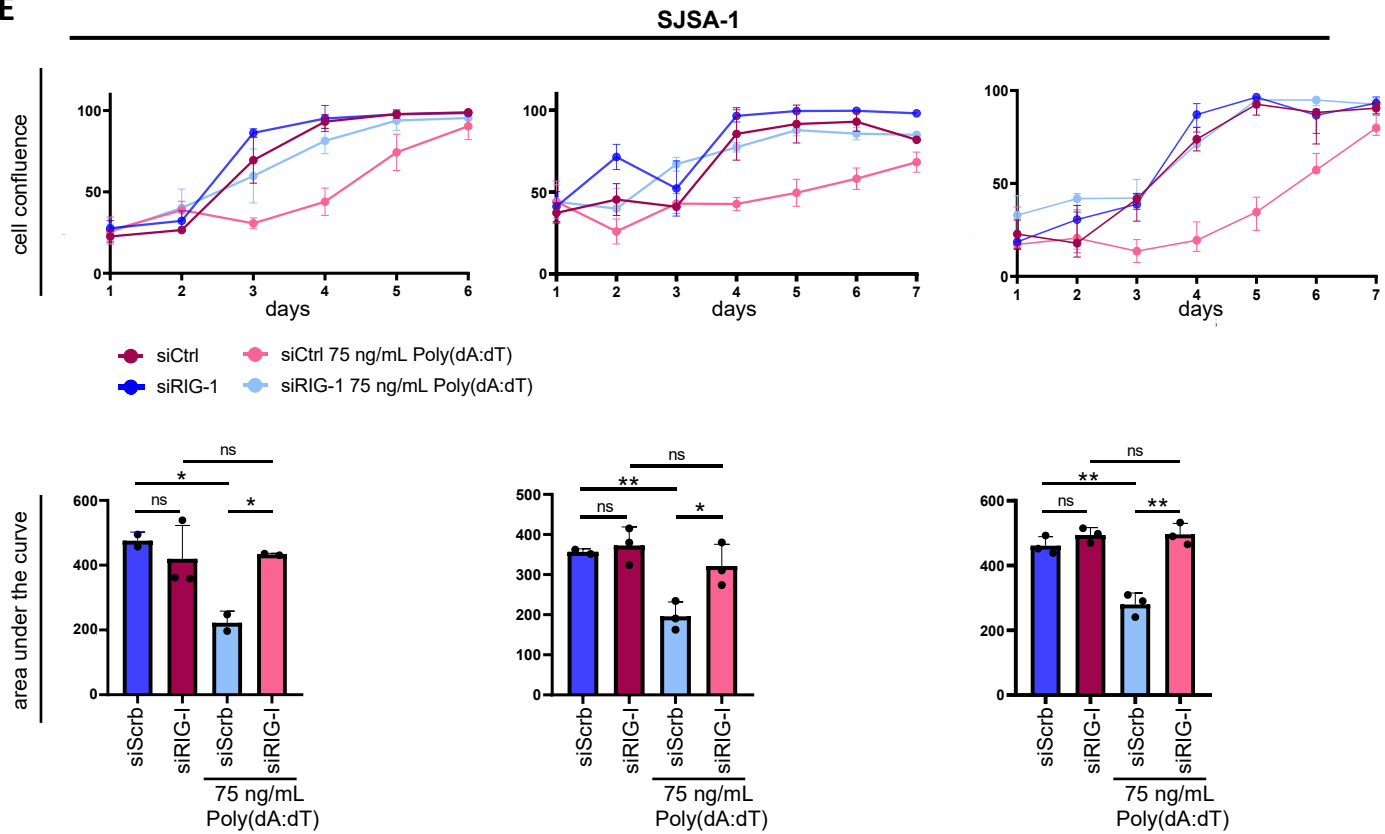
P



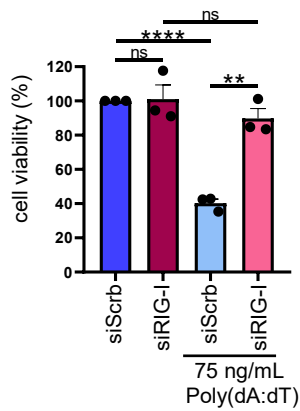




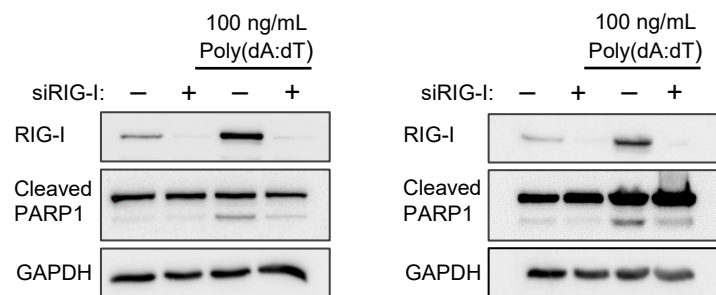
E



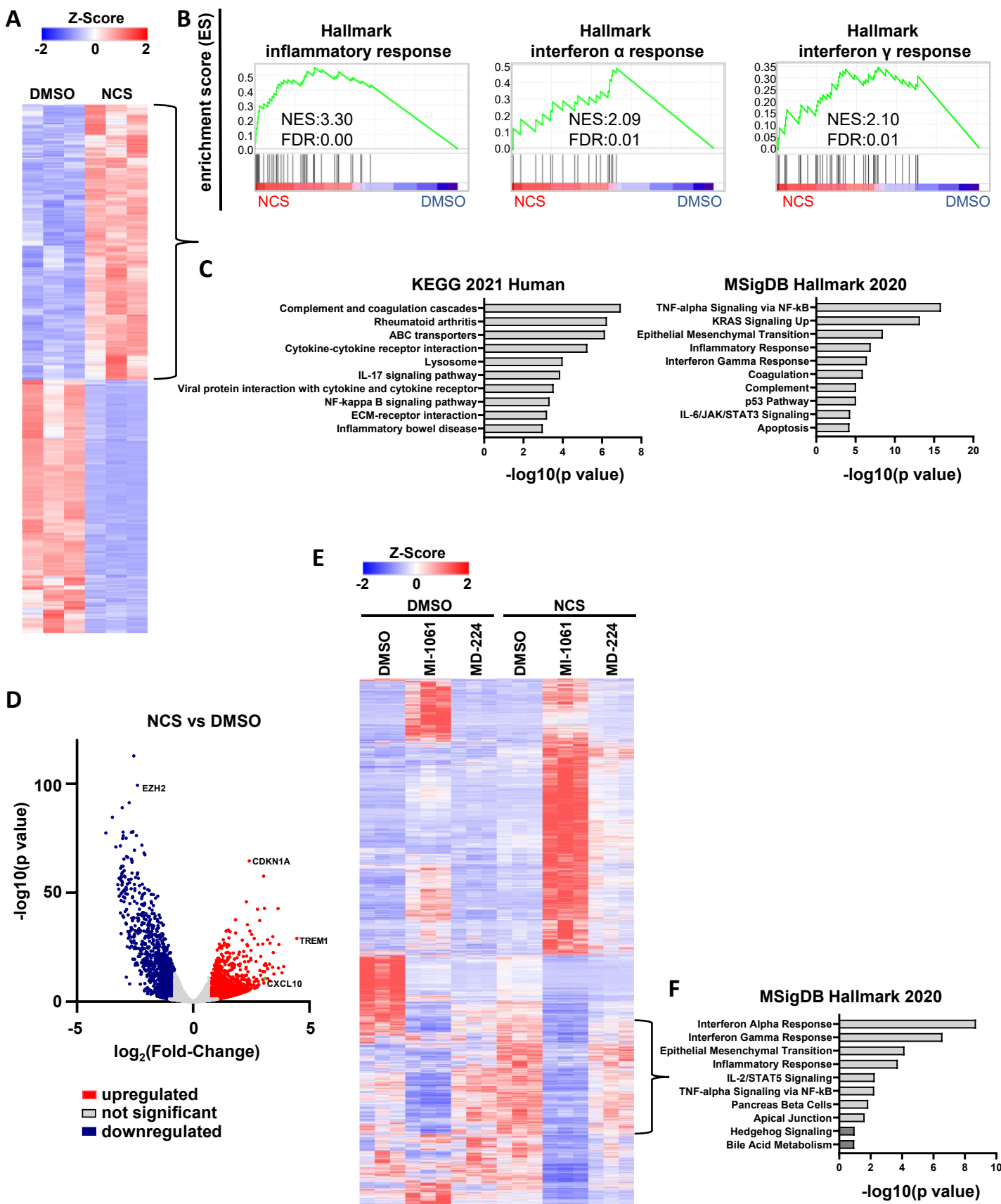
F



G

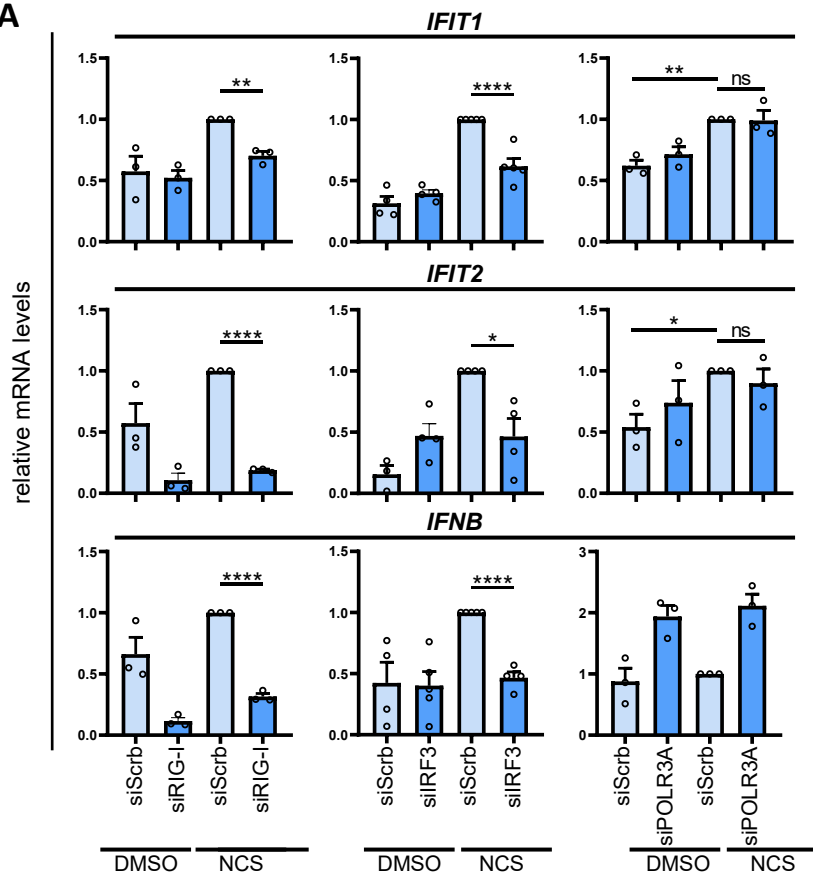


Suppl. Figure 7

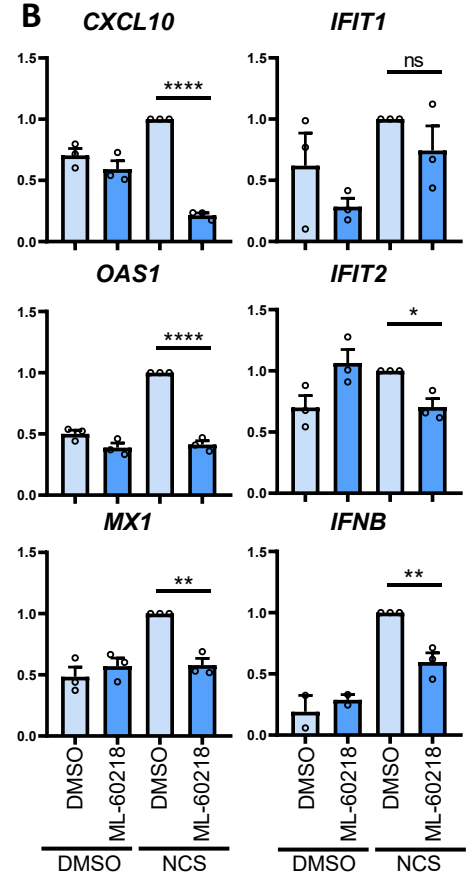


Suppl. Figure 8

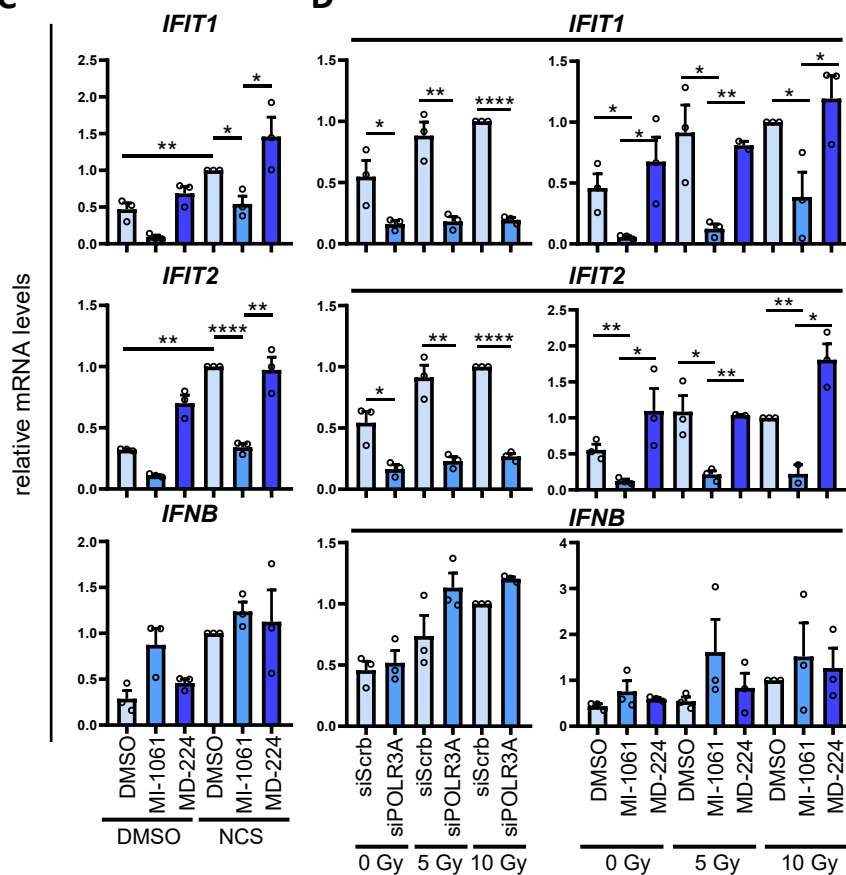
A



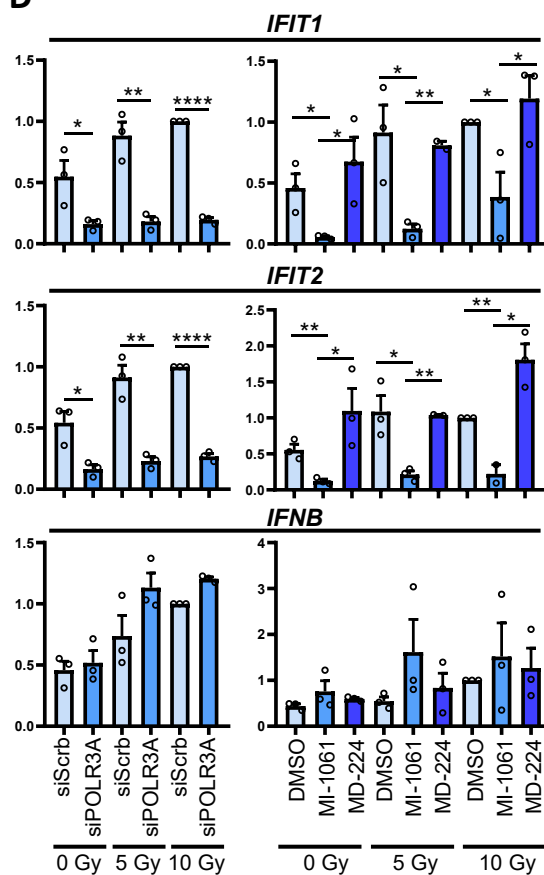
B



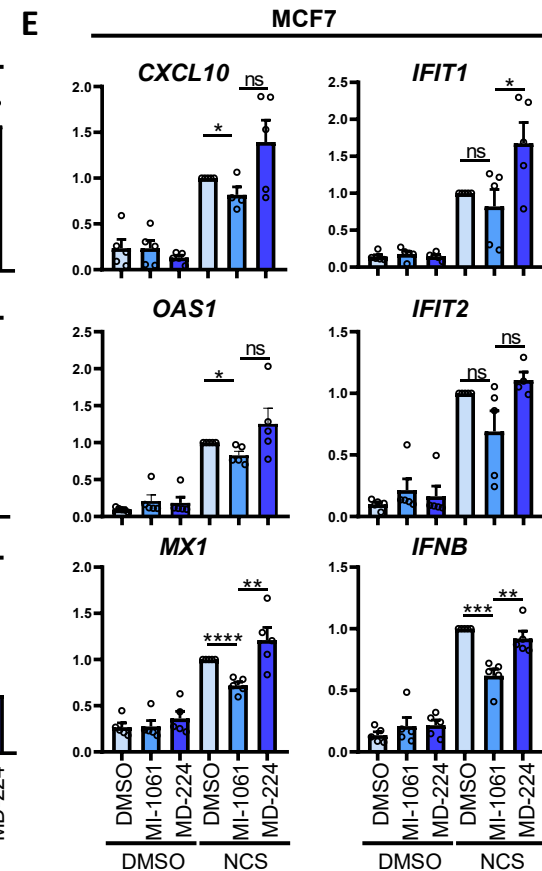
C



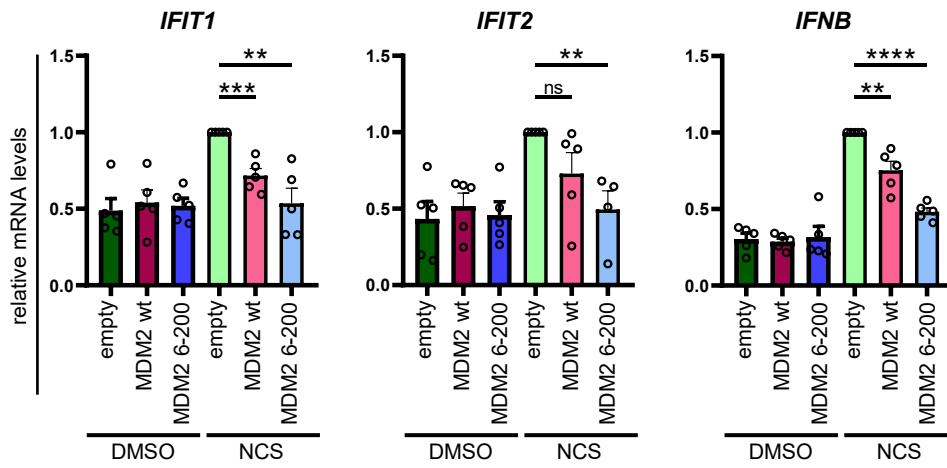
D



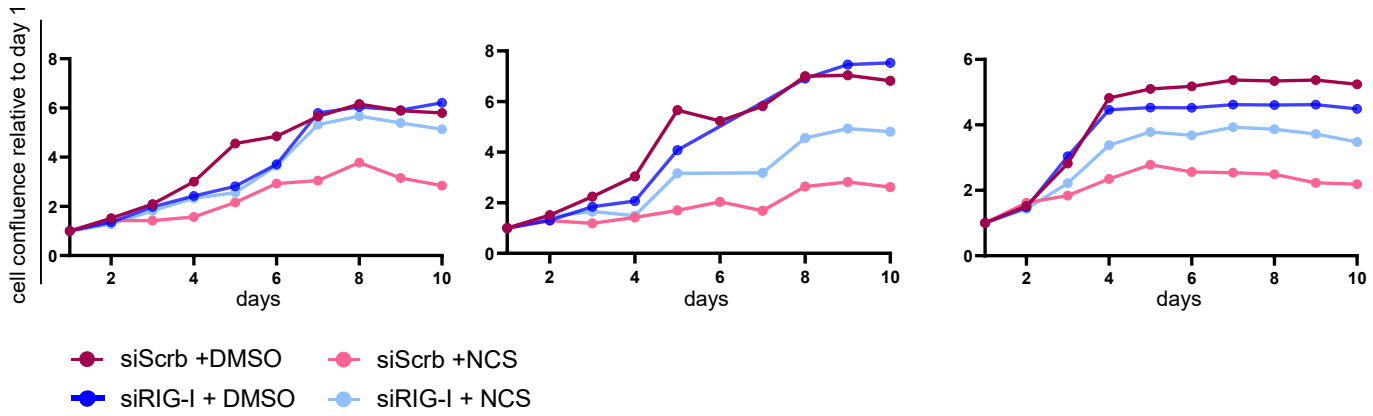
E



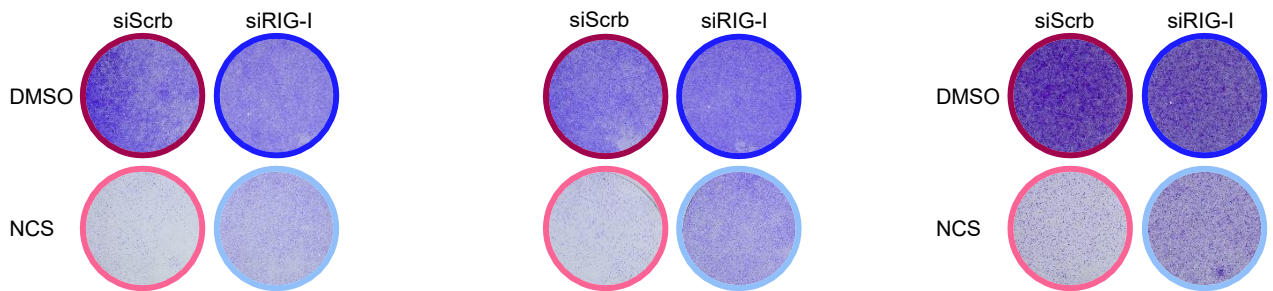
A



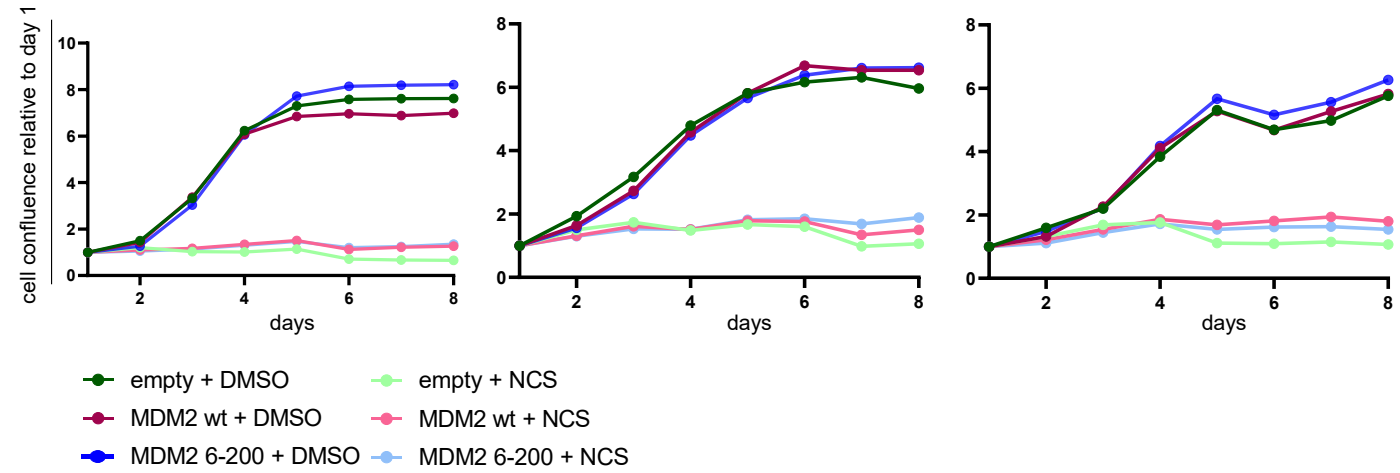
B



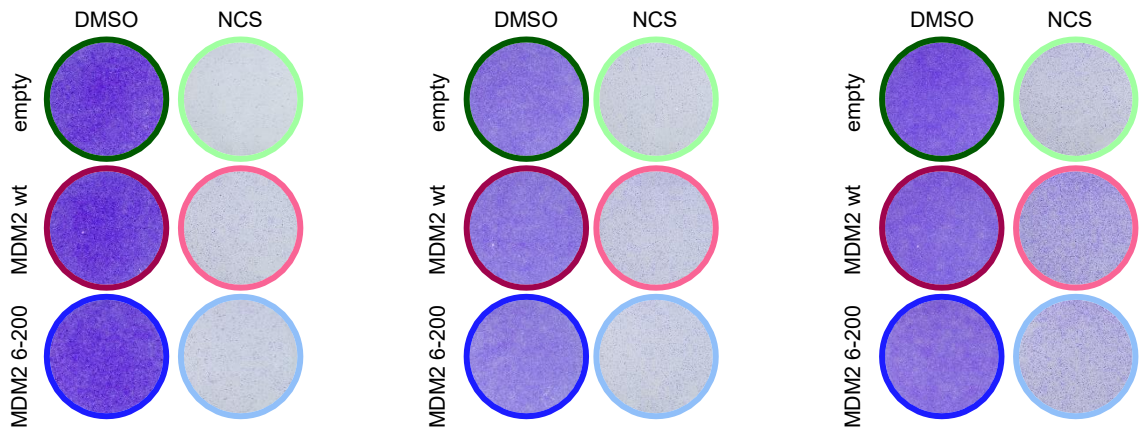
C



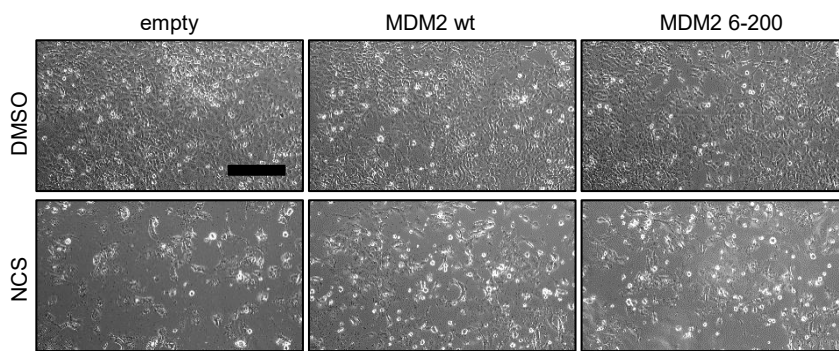
D



E

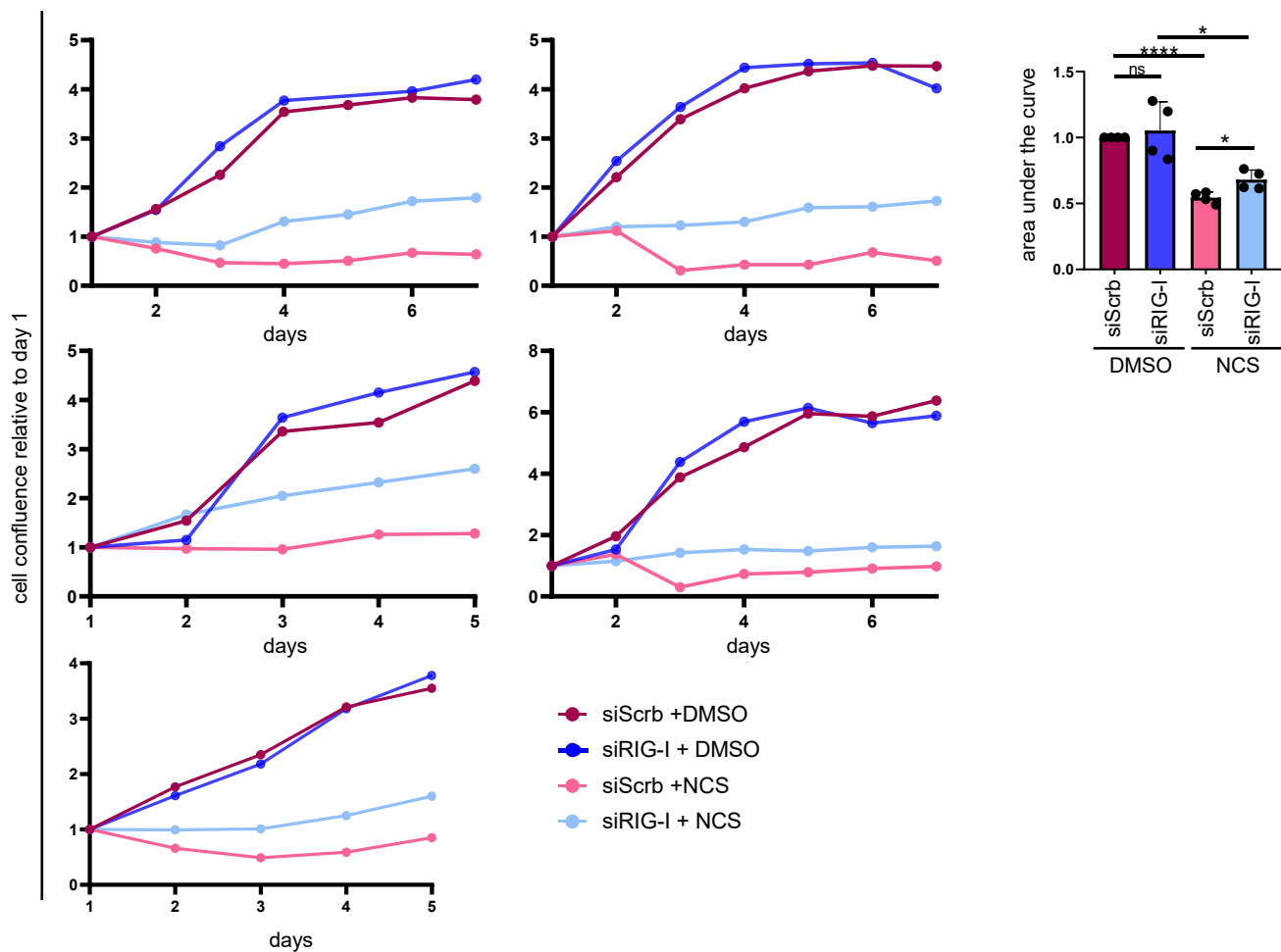


F

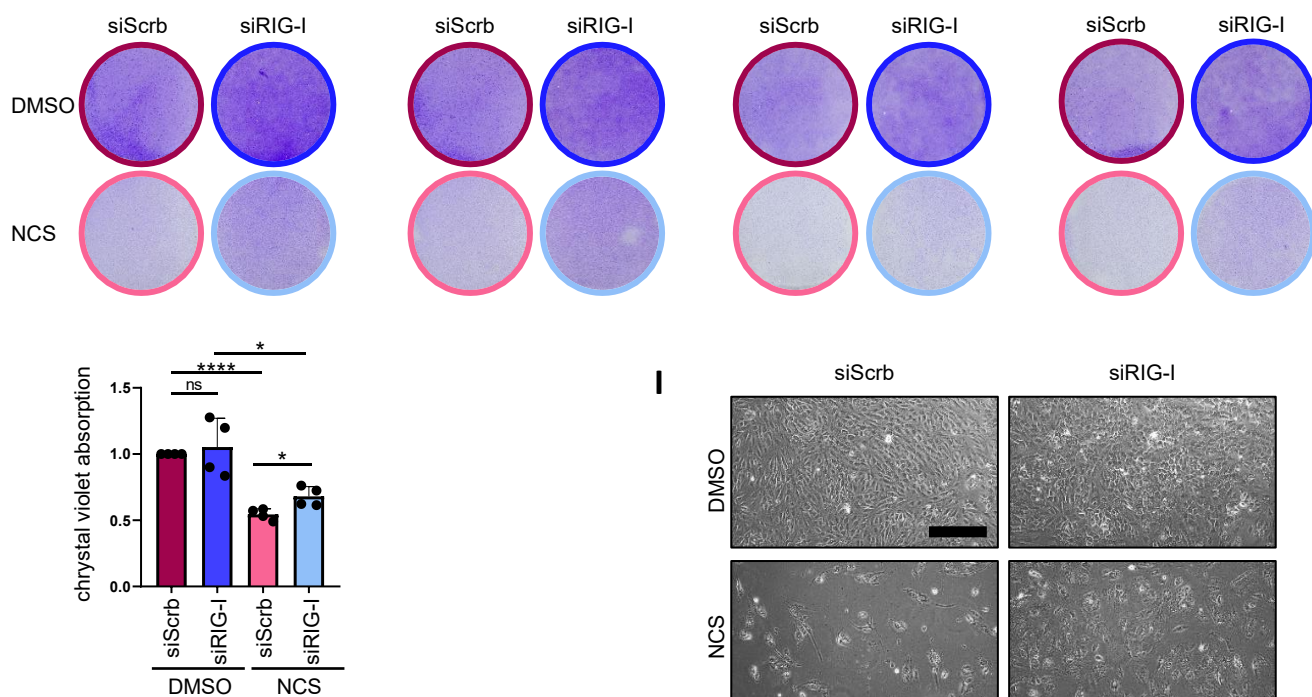


G

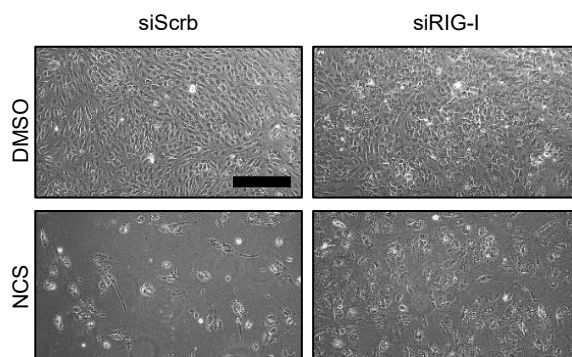
SJSA-1



H



I



Graphical abstract

