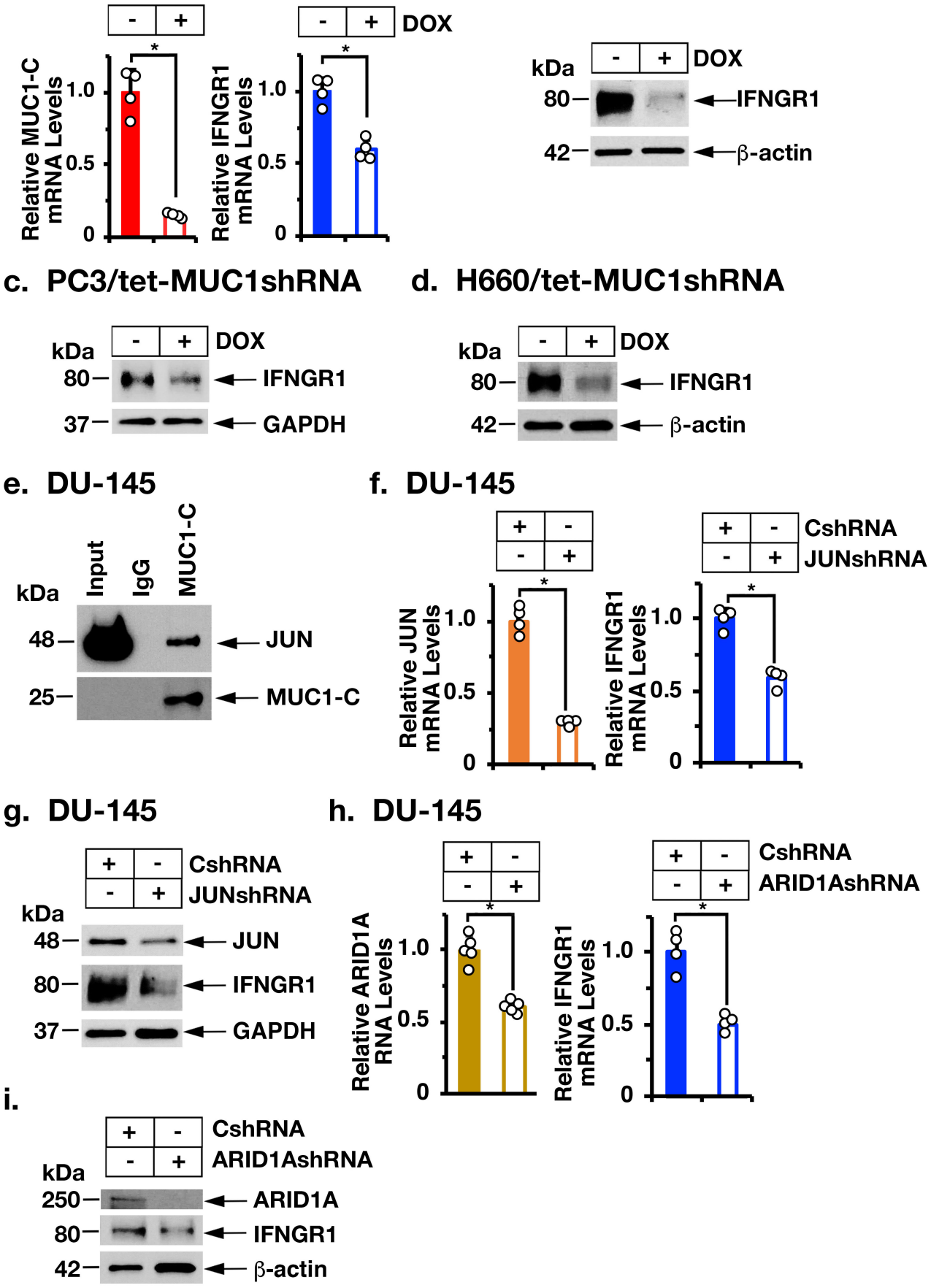
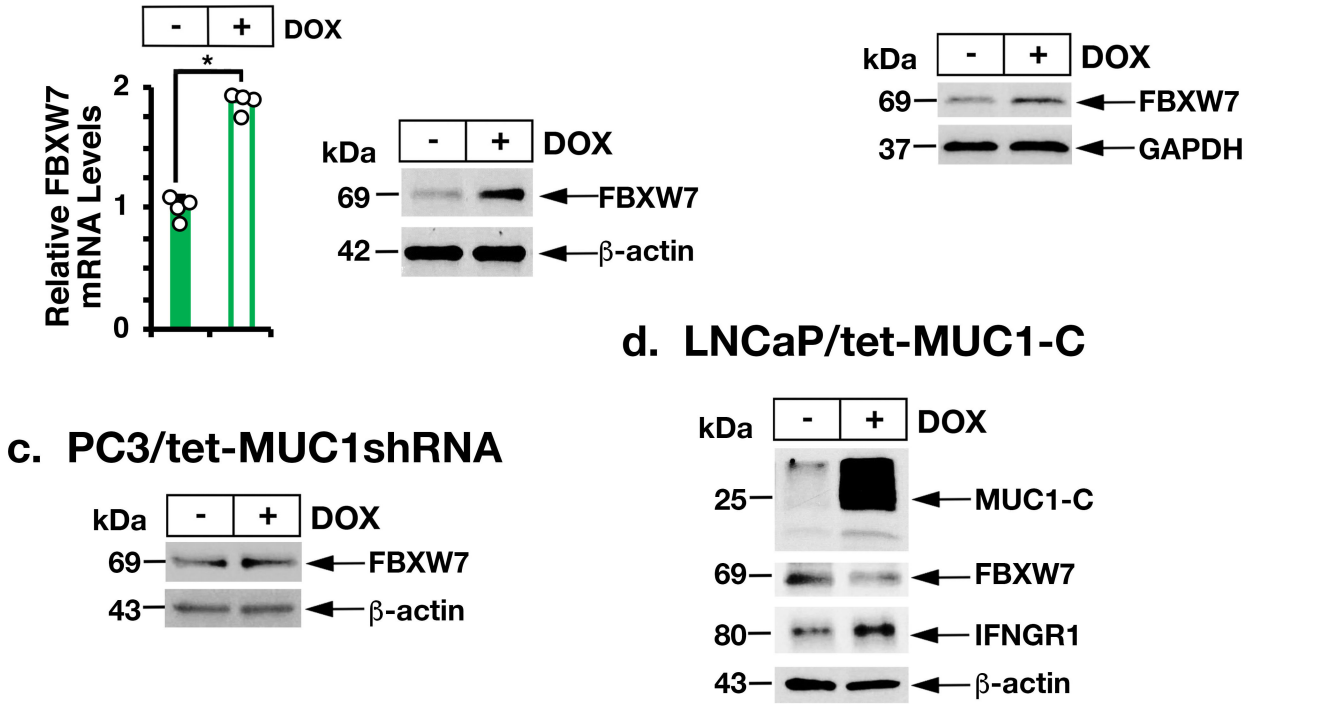
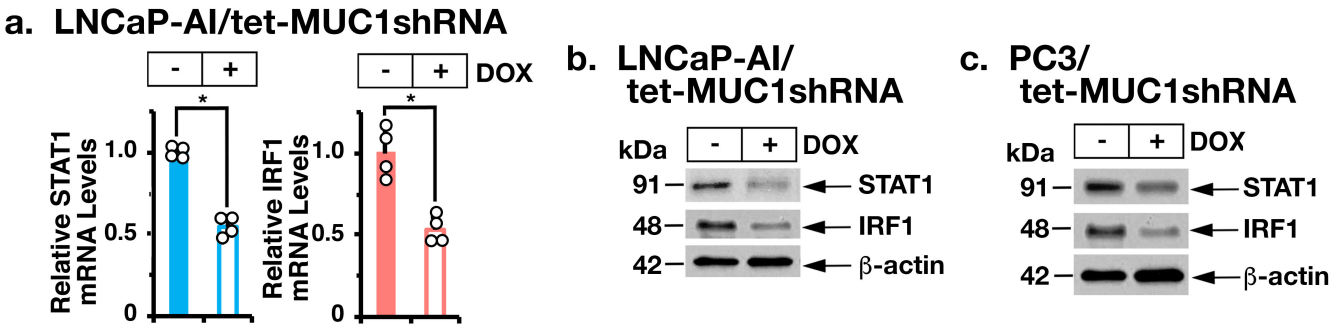

a. LNCaP-AI/tet-MUC1shRNA
b. LNCaP-AI/tet-MUC1shRNA
DOX
Relative MUC1-C mRNA Levels
Relative IFNGR1 mRNA Levels
kDa
80
IFNGR1
42
β-actin
c. PC3/tet-MUC1shRNA
d. H660/tet-MUC1shRNA
37
GAPDH
e. DU-145
Input
IgG
MUC1-C
48
JUN
25
MUC1-C
f. DU-145
CshRNA
JUNshRNA
Relative JUN mRNA Levels
g. DU-145
h. DU-145
ARID1AshRNA
Relative ARID1A RNA Levels
i.
250
ARID1A

Supplemental Fig. S1. Silencing MUC1-C and ARID1A suppresses IFNGR1 expression in CRPC/NEPC cells. (a). LNCaP-AI/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were analyzed for the indicated mRNA levels by qRT-PCR using primers listed in Supplemental Table S1. The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for vehicle-treated cells (assigned a value of 1). (**b-d).** Lysates from LNCaP-AI/tet-MUC1shRNA (**b**), PC3/tet-MUC1shRNA (**c**) and NCI-H660/tet-MUC1shRNA (**d**) cells treated with vehicle or DOX for 7 days were immunoblotted with antibodies against the indicated proteins. (**e).** Nuclear lysates from DU-145 cells were precipitated with a control IgG or anti-MUC1-C. The input and precipitated proteins were immunoblotted with antibodies against the indicated proteins. (**f and g).** DU-145 cells expressing a CshRNA or JUNshRNA were analyzed for the indicated mRNA levels by qRT-PCR (**f**). The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for CshRNA expressing cells (assigned a value of 1). Lysates were immunoblotted with antibodies against the indicated proteins (**g**). **(h and i).** DU-145 cells expressing a CshRNA or ARID1AshRNA were analyzed for the indicated mRNA levels by qRT-PCR (**h**). The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for CshRNA expressing cells (assigned a value of 1). Lysates were immunoblotted with antibodies against the indicated proteins (**i**).

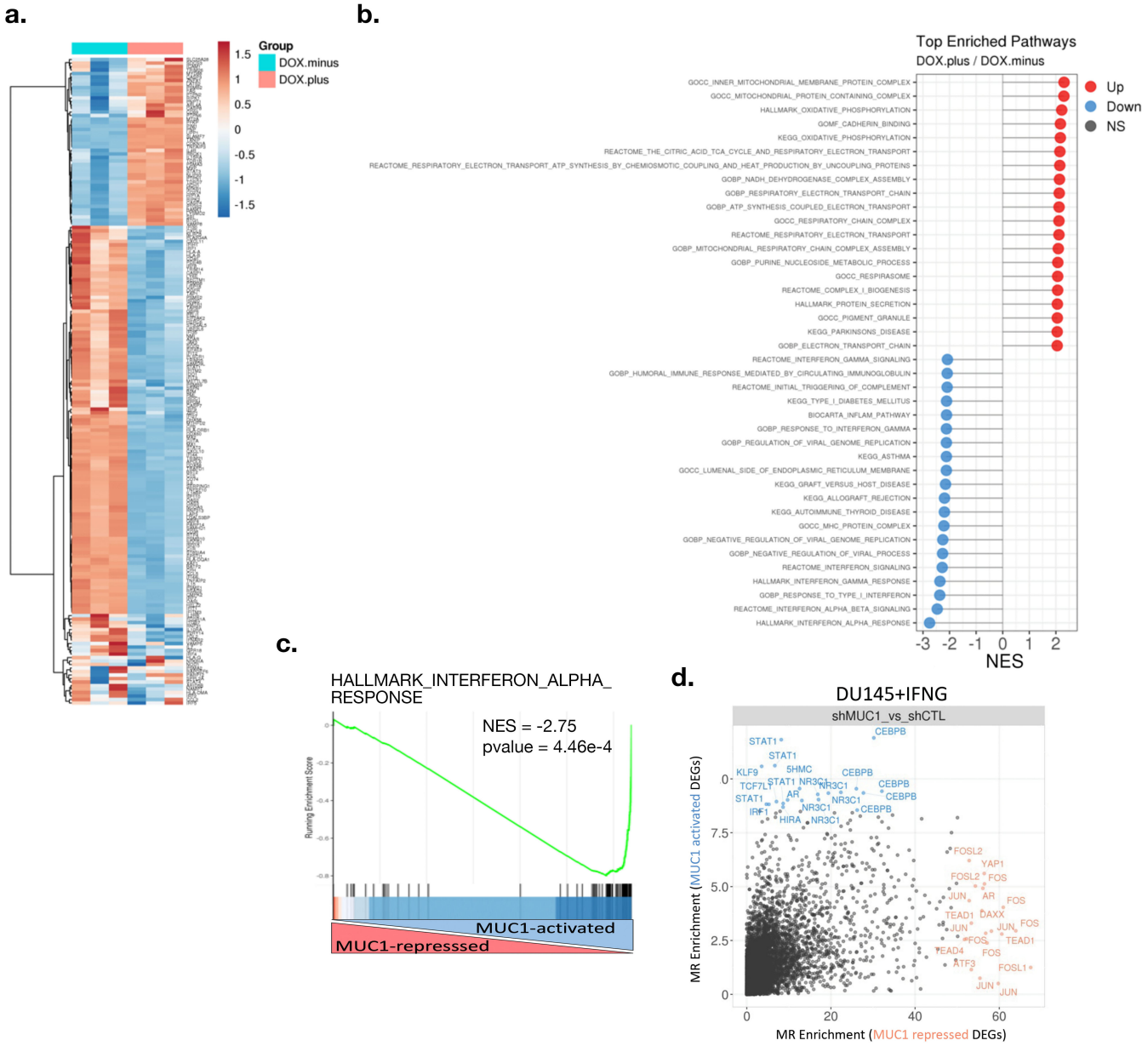


Supplemental Fig. S2. MUC1-C and NuRD suppress FBXW7 expression in CRPC/NEPC cells. (a). LNCaP-AI/tet-MUC1shRNA treated with vehicle or DOX for 7 days were analyzed for LBXW7 mRNA levels by qRT-PCR (left). The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for vehicle-treated cells (assigned a value of 1). Lysates were immunoblotted with antibodies against the indicated proteins (right). **(b and c).** Lysates from NCI-H660/tet-MUC1shRNA (**b**) and PC3/tet-MUC1shRNA (**c**) cells treated with vehicle or DOX for 7 days were immunoblotted with antibodies against the indicated proteins. **(d).** Lysates from LNCaP/tet-MUC1-C cells treated with vehicle or DOX for 7 days were immunoblotted with antibodies against the indicated proteins. **(e).** Lysates from LNCaP-AI/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were immunoblotted with antibodies against the indicated proteins. **(f).** DU-145 cells expressing a CshRNA, MTA1shRNA (left) or

MBD3shRNA (right) were analyzed for FBXW7 mRNA levels by qRT-PCR. The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for CshRNA expressing cells (assigned a value of 1).

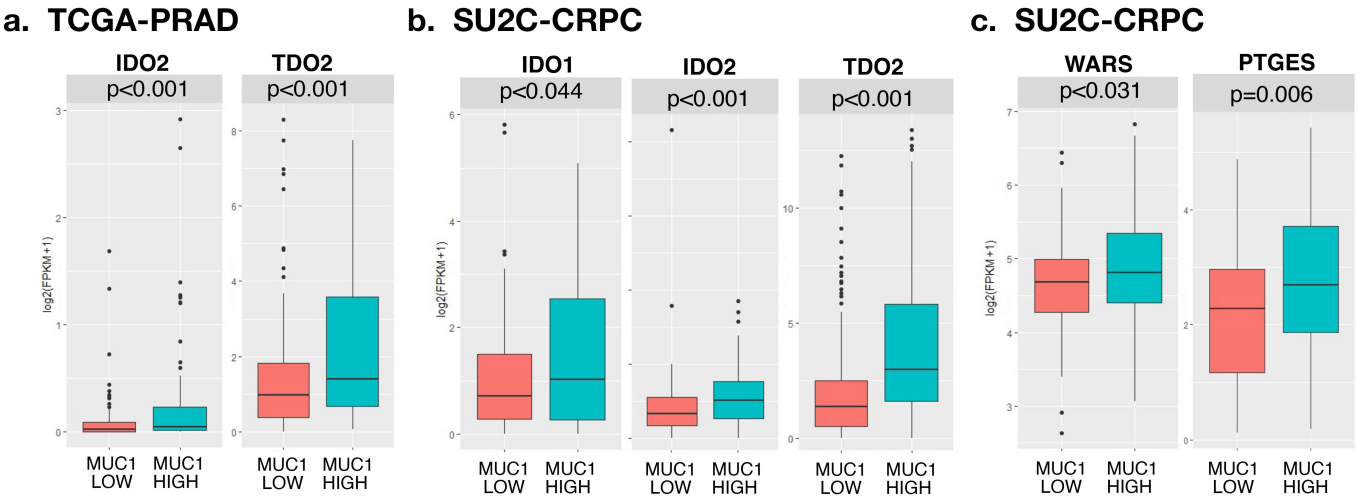


Supplemental Fig. S3. MUC1-C is necessary for STAT1 and IRF1 expression. (a and b). LNCaP-AI/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were analyzed for the indicated mRNA levels by qRT-PCR (**a**). The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for vehicle-treated cells (assigned a value of 1). Lysates were immunoblotted with antibodies against the indicated proteins (**b**). (**c**). Lysates from PC3/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were immunoblotted with antibodies against the indicated proteins.

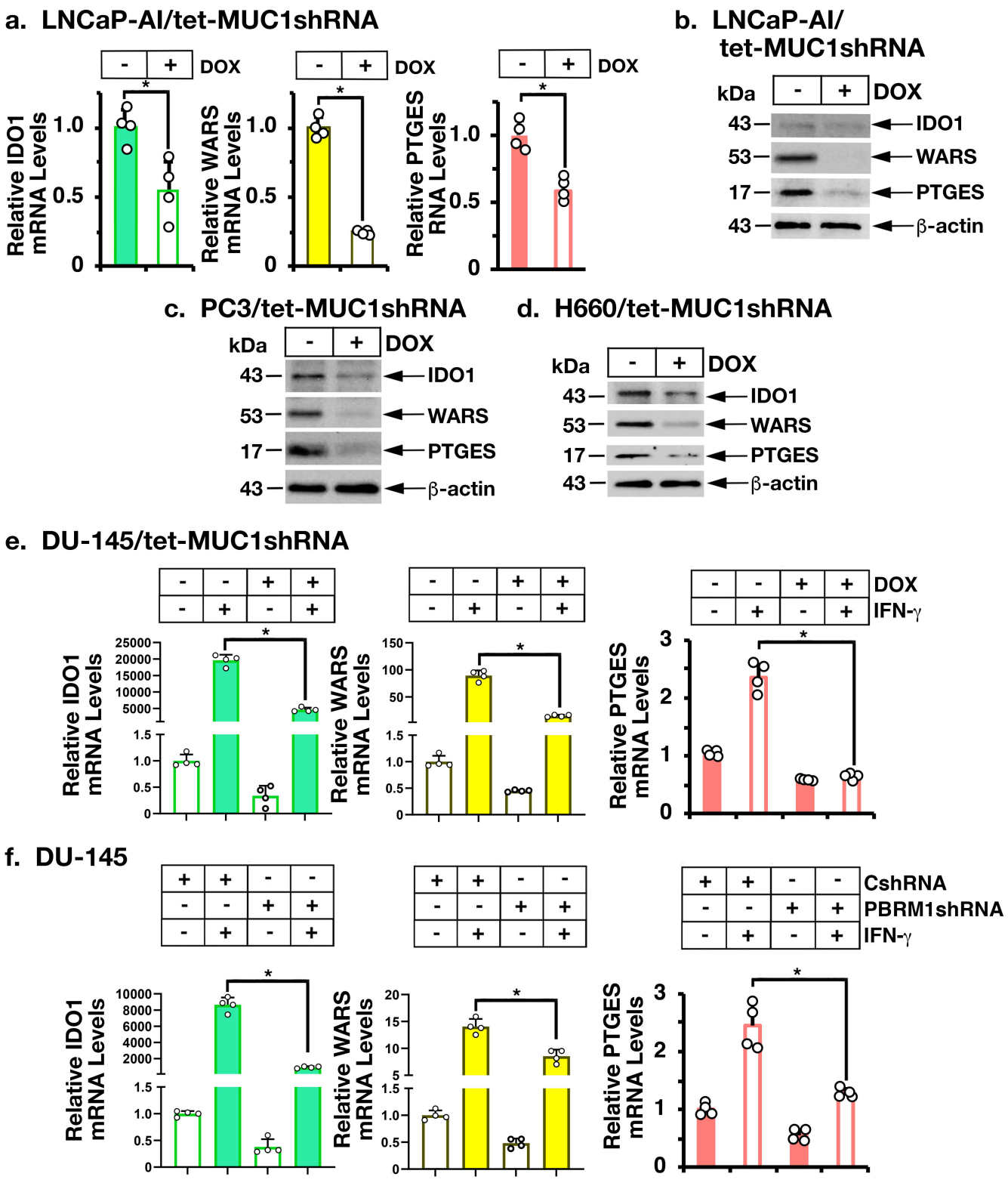


Supplemental Fig. S4. MUC1-C is necessary for induction of IFN-γ-stimulated gene sets. RNA-seq was performed in triplicates on DU-145/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days and then stimulated with 10 ng/ml IFN-γ for 24 hours. (**a**). Heatmap representing all genes from within the HALLMARK INTERFERON GAMMA RESPONSE pathway. Significant DEGs are shown as row annotations (downregulated = teal, upregulated = gold). (**b**). Top 30 significantly enriched pathways activated (top) and suppressed (bottom) by MUC1 silencing. (**c**). Analysis by GSEA using the HALLMARK INTERFERON ALPHA RESPONSE gene signature comparing DOX-treated with vehicle-treated cells. (**d**). Epigenetic Landscape in Silico deletion Analysis (LISA) was applied to the top 500 downregulated (MUC1-induced) and upregulated (MUC1-repressed) DEGs. Each data point represents the

significance level of regulatory potential of a given transcriptional factor derived from a unique ChIP-seq dataset. MUC1-activated genes are enriched for STAT1 and IRF1 in support of MUC1-C integrating the IFN-γ response by inducing the STAT1→IRF1 pathway. CEBPB is also enriched in the MUC1-activated gene set.

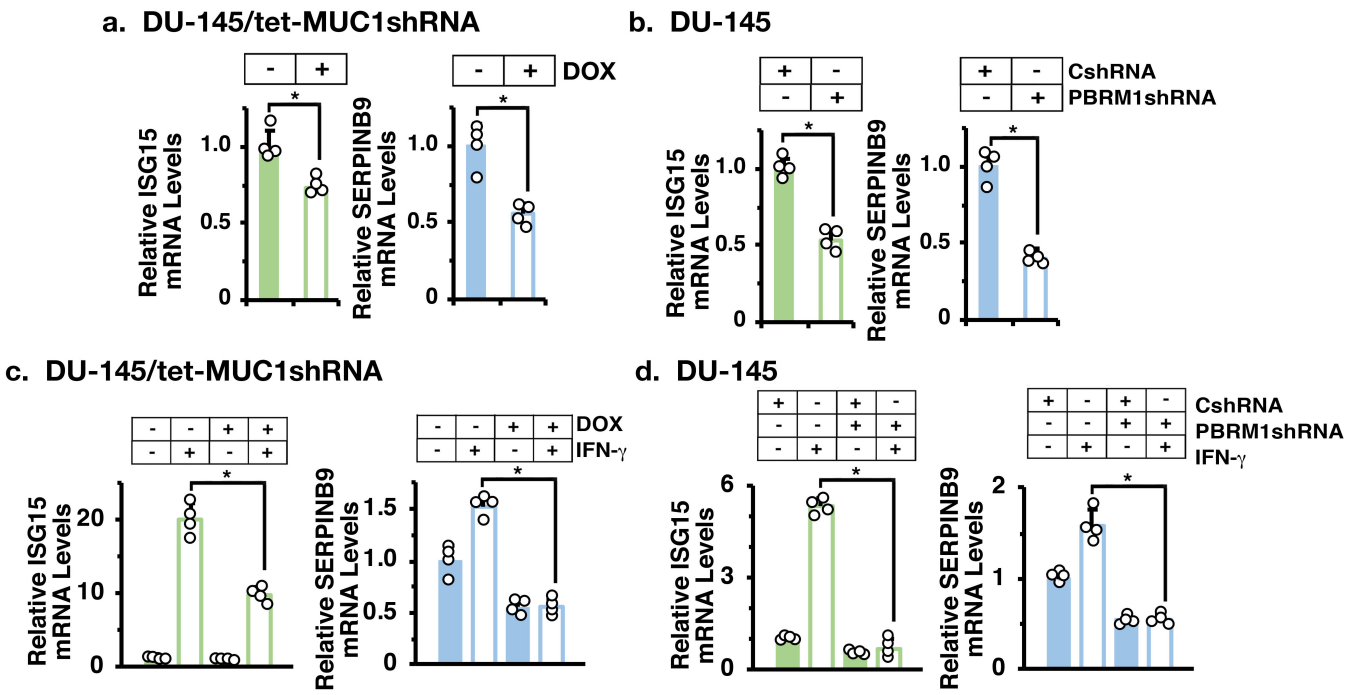


Supplemental Fig. S5. MUC1-high PCs associate with upregulation of IDO1, IDO2, TDO2, WARS and PTGES. (a-c). Expression of the indicated genes in the TCGA-PRAD (**a**) and SU2C-CRPC (**b,c**) cohorts was assessed in MUC1-high and MUC1-low groups using a Wilcoxon rank-sum test.

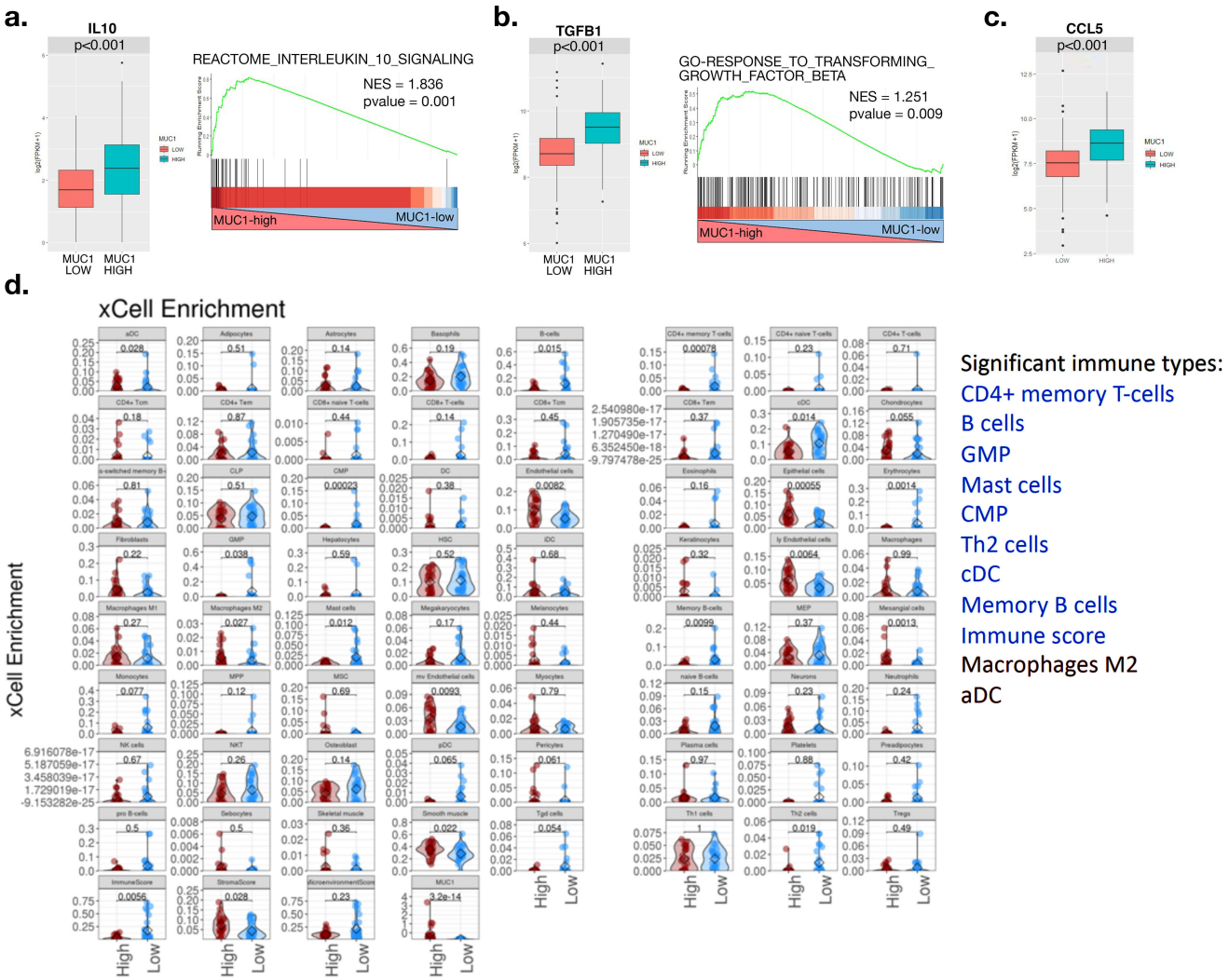


Supplemental Fig. S6. MUC1-C and PBRM1 are necessary for IDO1, WARS and PTGES expression. (a and b). LNCaP-AI/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were analyzed for the indicated mRNA levels by qRT-PCR (**a**). The results (mean±SD of 4 determinations) are expressed as relative mRNA levels compared to that obtained for vehicle-treated cells (assigned a value of 1). Lysates were

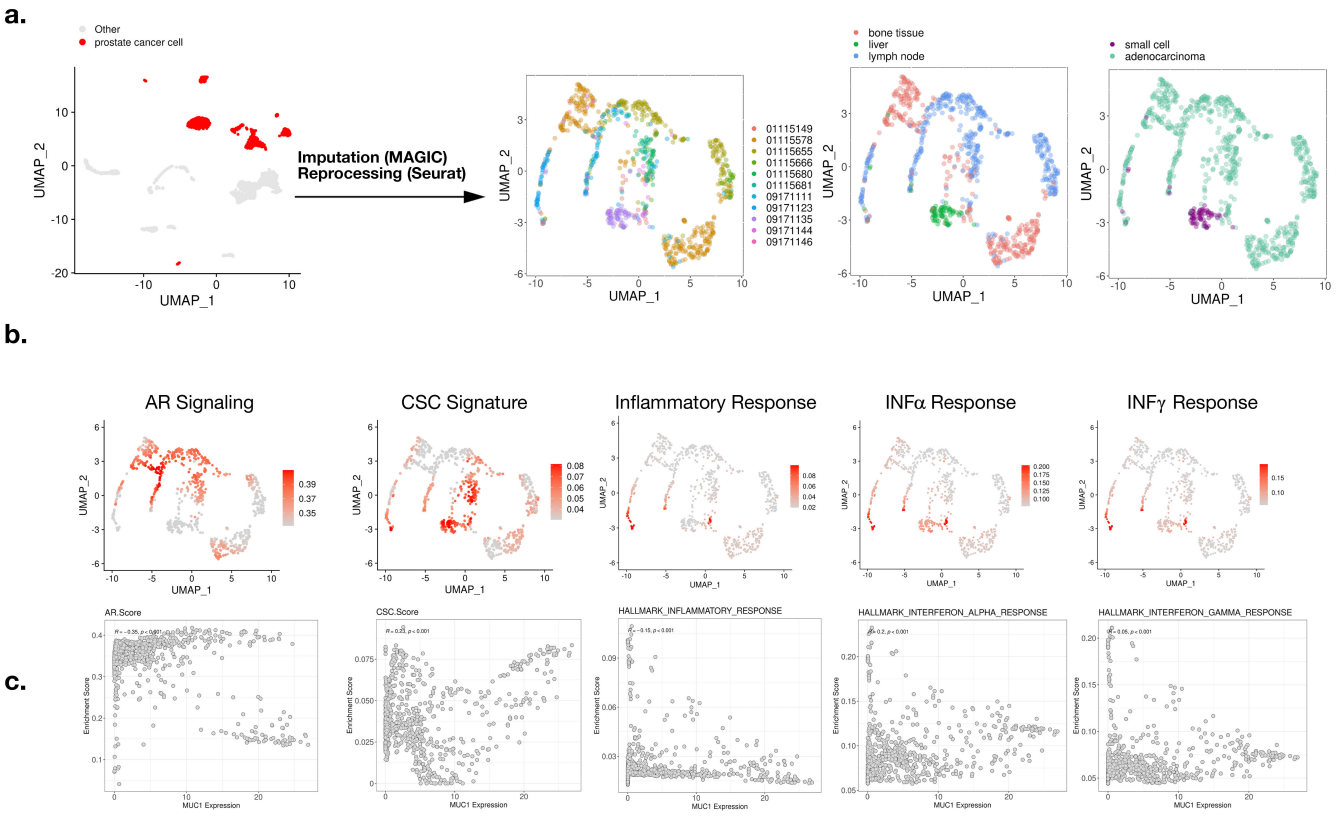
immunoblotted with antibodies against the indicated proteins (**b**). **(c and d).** Lysates from PC3/tet-MUC1shRNA (**c**) and NCI-H660/tet-MUC1shRNA (**d**) were immunoblotted with antibodies against the indicated proteins. **(e).** DU-145/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were stimulated with 10 ng/ml IFN-γ for 24 hours. The cells were analyzed for the indicated mRNA levels by qRT-PCR. The results (mean±SD of 3 determinations) are expressed as relative mRNA levels compared to that obtained for vehicle-treated cells (assigned a value of 1). (**f).** DU-145/CshRNA and DU-145/PBRM1shRNA were stimulated with 10 ng/ml IFN-γ for 24 hours. Lysates were immunoblotted with antibodies against the indicated protein.



Supplemental Fig. S7. MUC1 and PBRM1 are necessary for ISG15 and SERPINB9 expression. (a). DU-145/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were analyzed for the indicated mRNA levels by qRT-PCR. **(b).** DU-145/CshRNA and DU-145/PBRM1shRNA cells were analyzed for the indicated mRNA levels by qRT-PCR. **(c).** DU-145/tet-MUC1shRNA cells treated with vehicle or DOX for 7 days were stimulated with 10 ng/ml IFN-γ for 24 hours. The cells were analyzed for the indicated mRNA levels by qRT-PCR. **(d).** DU-145/CshRNA and DU-145/PBRM1shRNA cells stimulated with 10 ng/ml IFN-γ for 24 hours were analyzed for the indicated mRNA levels by qRT-PCR. The results (mean±SD of 3 determinations) are expressed as relative mRNA levels compared to that obtained for control cells (assigned a value of 1).



Supplemental Figure S8. MUC1-high PC tumors associate with (i) increased expression of IL-10, TGFB1 and CCL5, and (ii) depletion of immune effectors in the TME. (a). Expression of IL-10 in the TCGA-PRAD cohort was assessed in MUC1-high and MUC1-low groups using the Wilcoxon rank-sum test (left). Enrichment plot for the REACTOME INTERLEUKIN 10 SIGNALING pathway, comparing MUC1-high to MUC1-low PC tumors in the TCGA-PRAD cohort (right). **(b).** Expression of TGFB1 in the TCGA-PRAD cohort was assessed in MUC1-high and MUC1-low groups using the Wilcoxon rank-sum test (left). Enrichment plot for the GO RESPONSE TO TRANSFORMING GROWTH FACTOR BETA pathway, comparing MUC1-high to MUC1-low PC tumors in the TCGA-PRAD cohort (right). **(c).** Expression of CCL5 in the TCGA-PRAD cohort was assessed in MUC1-high and MUC1-low groups using the Wilcoxon rank-sum test. **(d).** Cell type estimates (xCell) of MUC1-high and MUC1-low CRPC tumors from the Beltran cohort.



Supplemental Figure S9. MUC1 associates with CSC and IFN signatures in CRPC cells. (a). Normalized and annotated scRNA-seq data from CRPC cells were obtained from He et al. CRPC cell expression was imputed using MAGIC and reprocessed for assessment of MUC1 across CRPC transcriptional phenotypes. **(b).** Single-cell enrichment was performed for curated AR and CSC signatures and select HALLMARK pathways. **(c).** Correlation analysis of Single-cell enrichment scores with MUC1 expression across CRPC cells.

Supplemental Table S1. Primers used for qRT-PCR.

MUC1-C	**FWD**	TACCGATCGTAGCCCCTATG
	REV	CTCACCAGCCCAAACAGG
IFNGR1	**FWD**	CTTTGGGTCAGAGTTAAAGCCA
	REV	TTCCATCTCGGCATACAGCAA
FBXW7	**FWD**	CGAACTCCAGTAGTATTGTGGACCT
	REV	TTCTTTTCATTTTTGT TGTTTTTGTATAGA
STAT1	**FWD**	GGAACTTGATGGCCCTAAAGGA
	REV	ACAGAGCCCACTATCCGAGACA
IRF1	**FWD**	CATGGCTGGGACATCAACAA
	REV	TTGTATCGGCCTGTGTGAATG
JUN	**FWD**	CCAAAGGATAGTGCGATGTTT
	REV	CTGTCCCTCTCCACTGCAAC
ARID1A	**FWD**	ACCTCTATCGCCTCTATGTGTCTGT
	REV	CTGGCAGCACTGCTTGATGT
IDO1	**FWD**	TCTCATTTCGTGATGGAGACT
	REV	GTGTCCCGTTCTTGCATTTGC
WARS	**FWD**	TGACGGATGACGAGAAGTATCT
	REV	GCCGAAAATGCCTTTCACTTG
PTGES	**FWD**	GGAAACTGCAAATGTCCCCTTGAT
	REV	CACATCTCAGGTCACGGGTCTA
ISG15	**FWD**	CGCAGATCACCCAGAAGATCG
	REV	TTCGTCGCATTTGTCCACCA
SERPINB9	**FWD**	TGGACCAAGCCAGACTGTATG
	REV	TGCACGAACTTGGACAGACA
GAPDH	**FWD**	CCAAGACCCTGATGAACACC
	REV	CCAAGACCCTGATGAACACC