Figure S1. TIP60 overexpression leads to the downregulation of UHRF1 and DNMT1 levels. (A and B) Immunostaining of UHRF1 and DNMT1 in HeLa cells. Either TIP60-eGFP WT or TIP60ΔMYST-eGFP mutant was transiently overexpressed. Cells were fixed following transfection and labeled with either anti-UHRF1 or anti-DNMT1 antibody and then with Alexa 568-labeled secondary antibody before visualization in confocal microscopy. Scale bar, 10 μm. eGFP-transfected cells served as a negative control. (C and D) Mean fluorescence intensities representing the levels of UHRF1 and DNMT1 in different samples. Values are the mean ± SEM for three independent experiments; ****P<0.0001 (vs. eGFP control group). One-way ANOVA with Tukey's post hoc test was used for analysis. UHRF1, ubiquitin-like, containing PHD and RING finger domains 1; TIP60, Tat interactive protein, 60 kDa; USP7, ubiquitin-specific-processing protease 7; DNMT1, DNA methyltransferase 1.

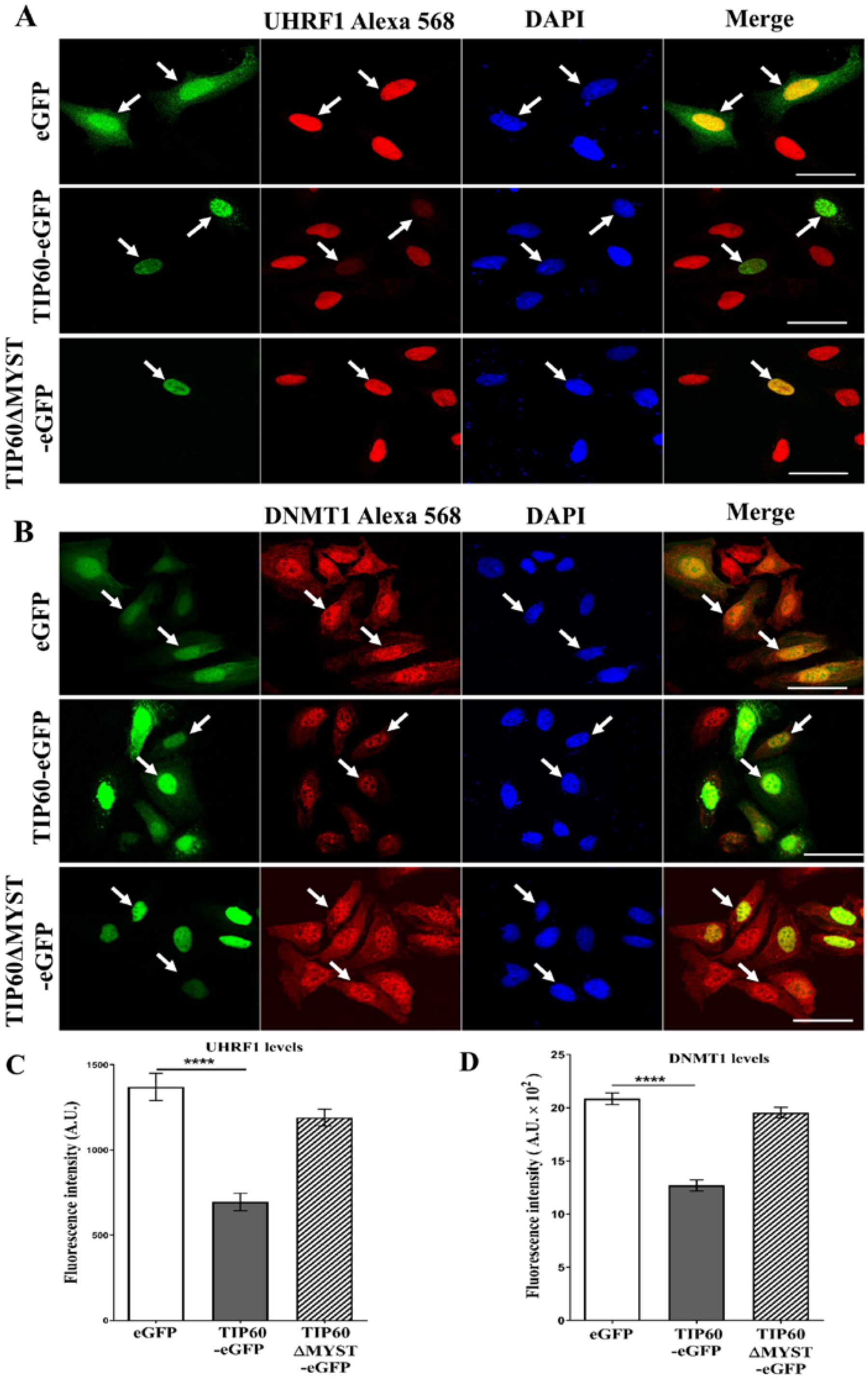


Figure S2. TIP60 overexpression leads to down-regulation of UHRF1 levels (lane 2, - MG-132) (A). One group of samples was treated with 10 μM of MG-132 (8 h before cell harvesting). MG-132 treatment lead to improvement in expression levels of UHRF1 in TIP60 transfected sample (lane 2, + MG-132). Of note, the ubiquitination bands and smear were also observed over UHRF1 in TIP60-transfected sample (lane 2, + MG-132). (B) UHRF1 bands were quantified and values are expressed as the mean ± SEM for three different experiments which were analyzed statistically by one-way ANOVA with Tukey's post hoc test. $^{*}P<0.05$; $^{****}P<0.0001$. UHRF1, ubiquitin-like, containing PHD and RING finger domains 1; TIP60, Tat interactive protein, 60 kDa.

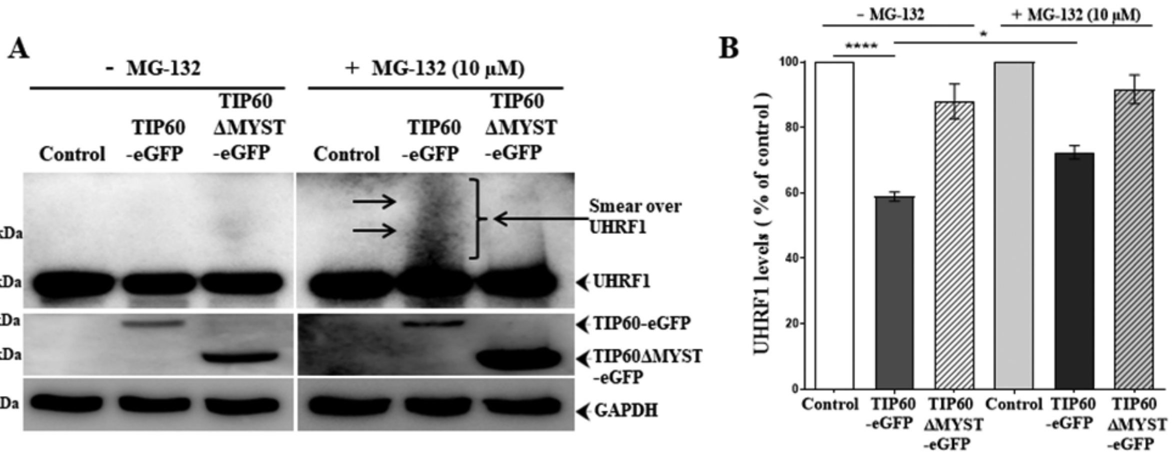


Figure S3. Interaction of UHRF1 and ubiquitin in the presence of the TIP60 inhibitor, NU9056, as monitored by FRET-FLIM. (A) Representative 30x30 μm FLIM images of HeLa cells stably expressing GFP-UHRF1 WT cells and co-transfected with RFP-ubiquitin. The lifetime values are shown by using a color code ranging from red (1.8 ns) to blue (2.5 ns). Scale bar, 10 μm. In comparison to cells expressing only (a) GFP-UHRF1 WT, a marked decrease in the GFP lifetime and thus, a strong FRET efficiency was observed when HeLa cells were (b) transfected with RFP-ubiquitin for 24 h. Following treatment with NU9056 at concentrations of 1, 3 and 5 μM (for 24 h), there was still a considerable FRET (c, d and e), while no FRET was observed for cells treated with 10, 30 and 100 μM concentration (for 24 h) of NU9056 (f, g and h). FLIM data indicate that the TIP60-promoted interaction of UHRF1 with ubiquitin is impaired when the acetyltransferase activity of TIP60 was inhibited by NU9056. (B) Plot of GFP-UHRF1 lifetime as a function of NU9056 concentration. Values are the mean ± SEM from two independent experiments. The point at 0 concentration corresponds to the lifetime of GFP-UHRF1 WT co-transfected with RFP-Ubiquitin in the absence of NU9056. FRET efficiency was calculated according to $E=1-(\tau_{DA}/\tau_{D})$, where τ_{DA} is the lifetime of the donor (GFP) in the presence of acceptor (RFP) and τ_{D} is the lifetime of GFP in the absence of acceptor. UHRF1, ubiquitin-like, containing PHD and RING finger domains 1; TIP60, Tat interactive protein, 60 kDa; FRET, Förster Resonance Energy Transfer.

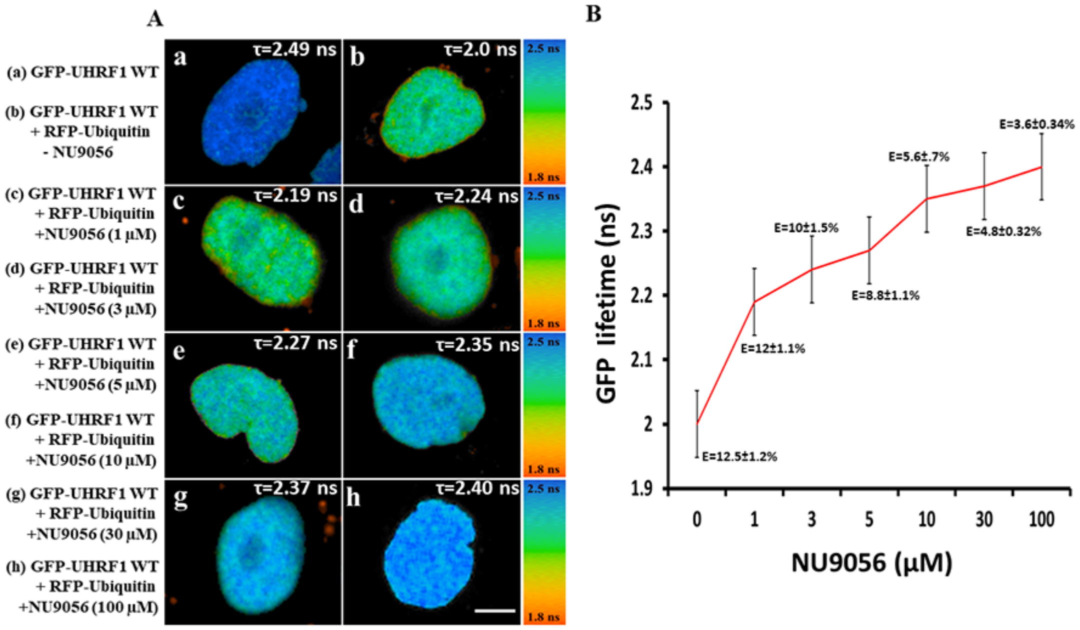


Figure S4. Box plot representing the distribution of the expression of TIP60 (KAT5) in TCGA cancers in comparison to non-tumor samples. Red circle indicates the mean expression of TIP60 (KAT5) in corresponding non-tumor samples. TIP60, Tat interactive protein, 60 kDa. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.

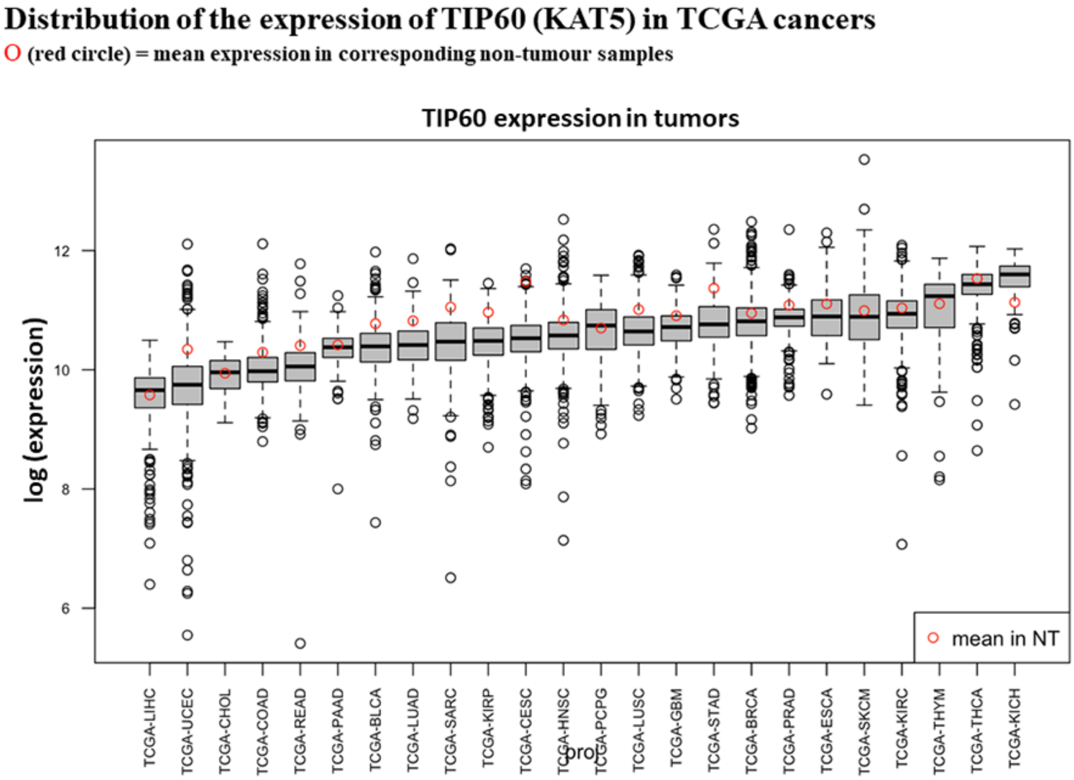
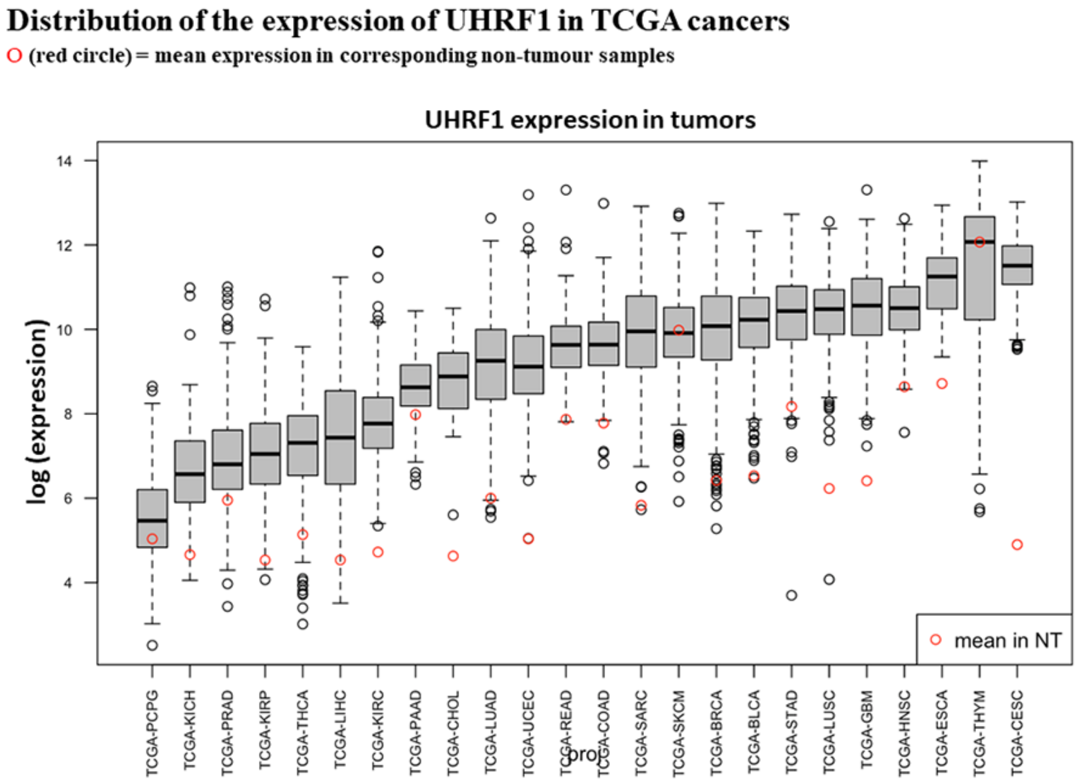


Figure S5. Box plot representing the distribution of the expression of UHRF1 in TCGA cancers in comparison to non-tumor samples. Red circle indicates the mean expression of UHRF1 in corresponding non-tumor samples. UHRF1, ubiquitin-like, containing PHD and RING finger domains 1. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.



Distribution of the expression of UHRF1 in TCGA cancers

○ (red circle) = mean expression in corresponding non-tumour samples

UHRF1 expression in tumors

Figure S6. Survival plots representing the association between TIP60/KAT5 expression and survival probability in TCGA cancers (KIRC, LGG). The y-axis represents proportion of survival and the x-axis represents survival time (months). TIP60, Tat interactive protein, 60 kDa. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.

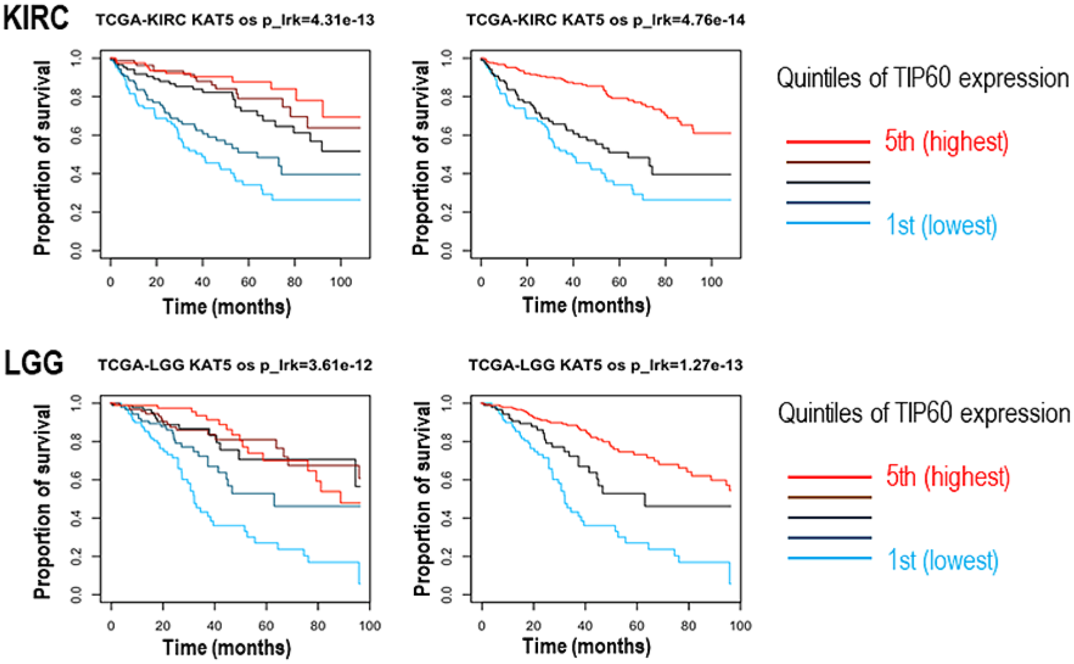


Figure S7. Survival plots representing the association between UHRF1 expression and survival probability in TCGA cancers. The y-axis represents the proportion of survival and the x-axis represents survival time (months). UHRF1, ubiquitin-like, containing PHD and RING finger domains 1. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.

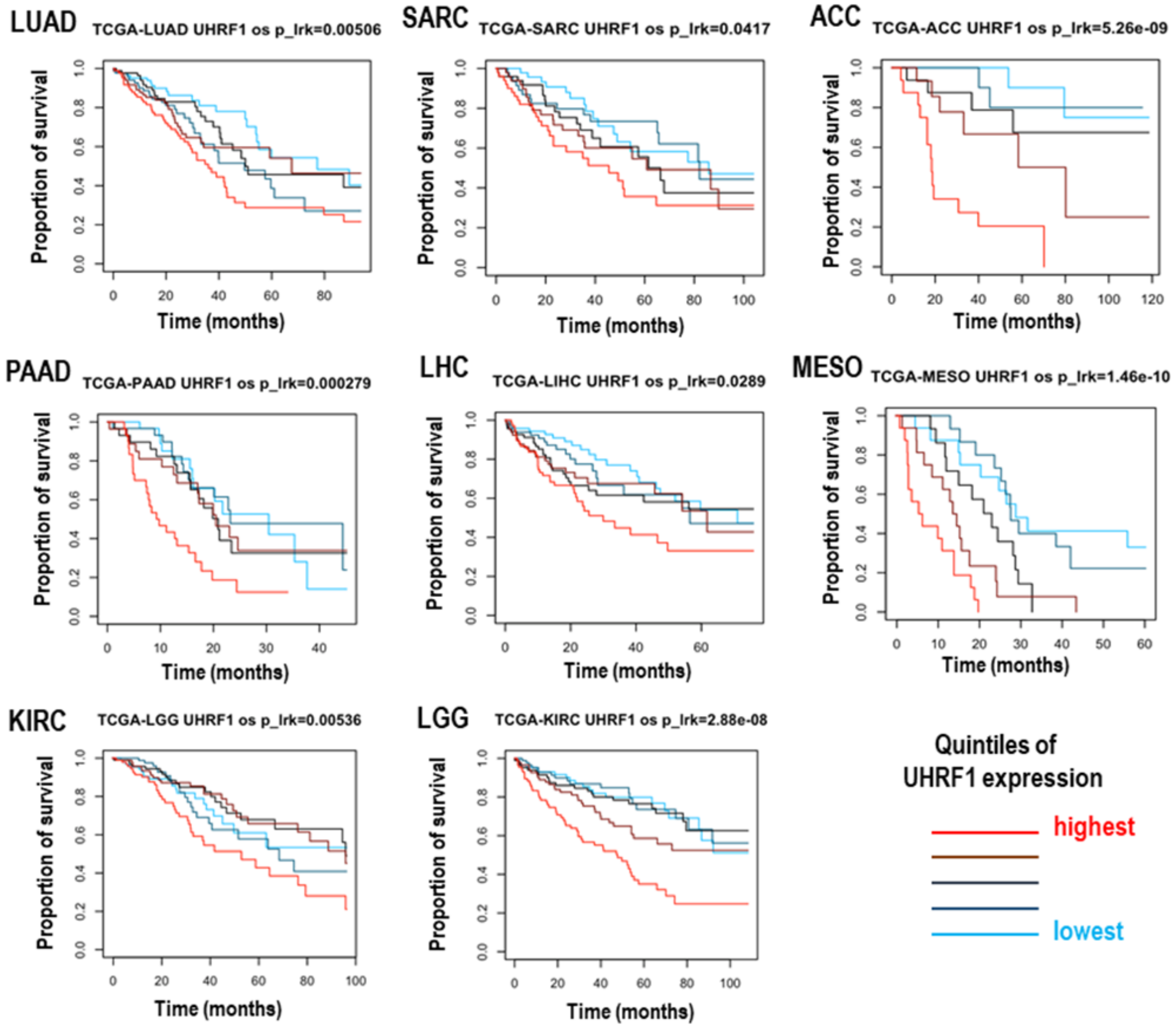


Figure S8. Samples are plotted according to the expression of TIP60/KAT5 (y-axis) and UHRF1 (x-axis) in each of the TCGA cancer types (KIRC, LGG) and effect of this expression on survival. Cancer samples are in red and non-tumor samples in blue. UHRF1, ubiquitin-like, containing PHD and RING finger domains 1; TIP60, Tat interactive protein, 60 kDa. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.

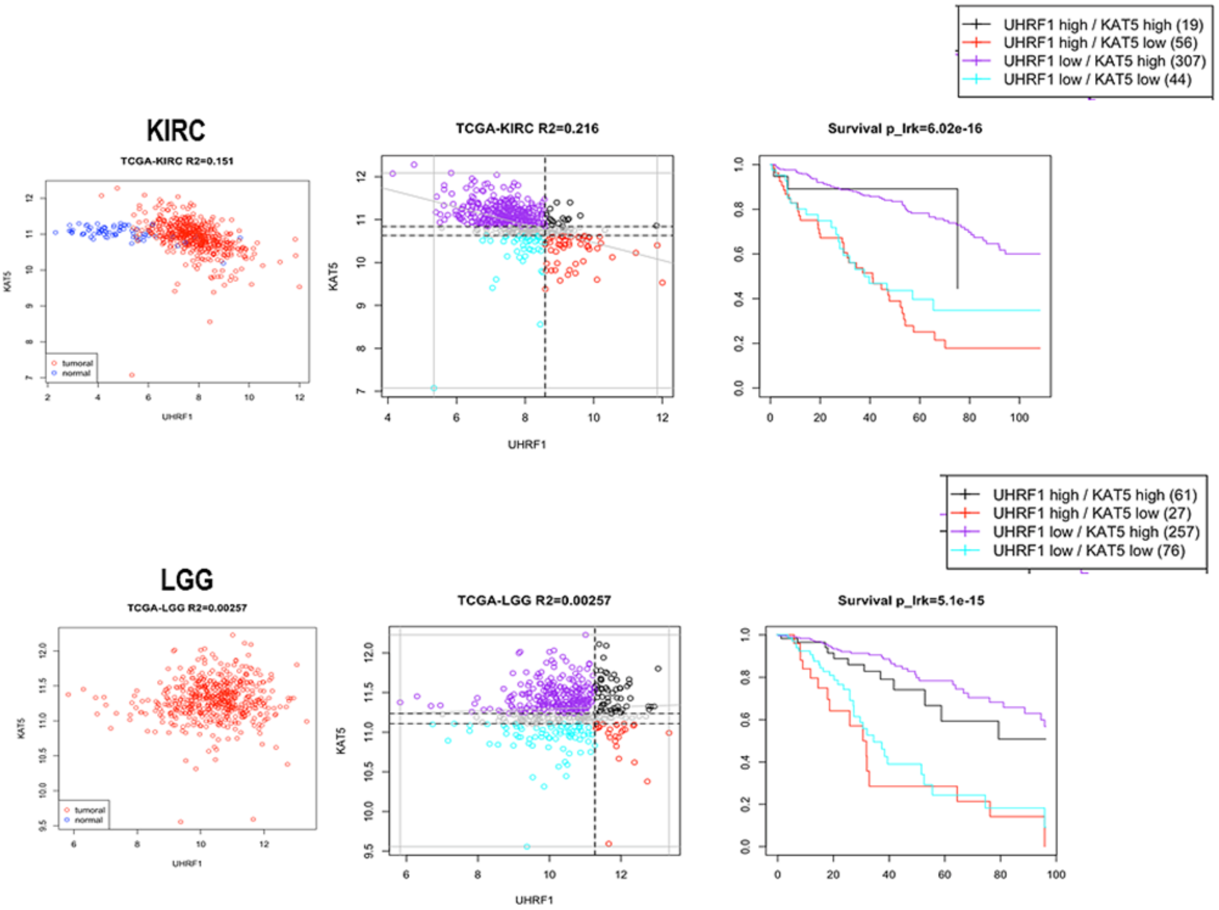


Figure S9. Box plot representing the distribution of the expression of USP7 in TCGA cancers in comparison to non-tumor samples. Red circle indicates mean expression of USP7 in corresponding non-tumor samples. USP7, ubiquitin-specific-processing protease 7. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.

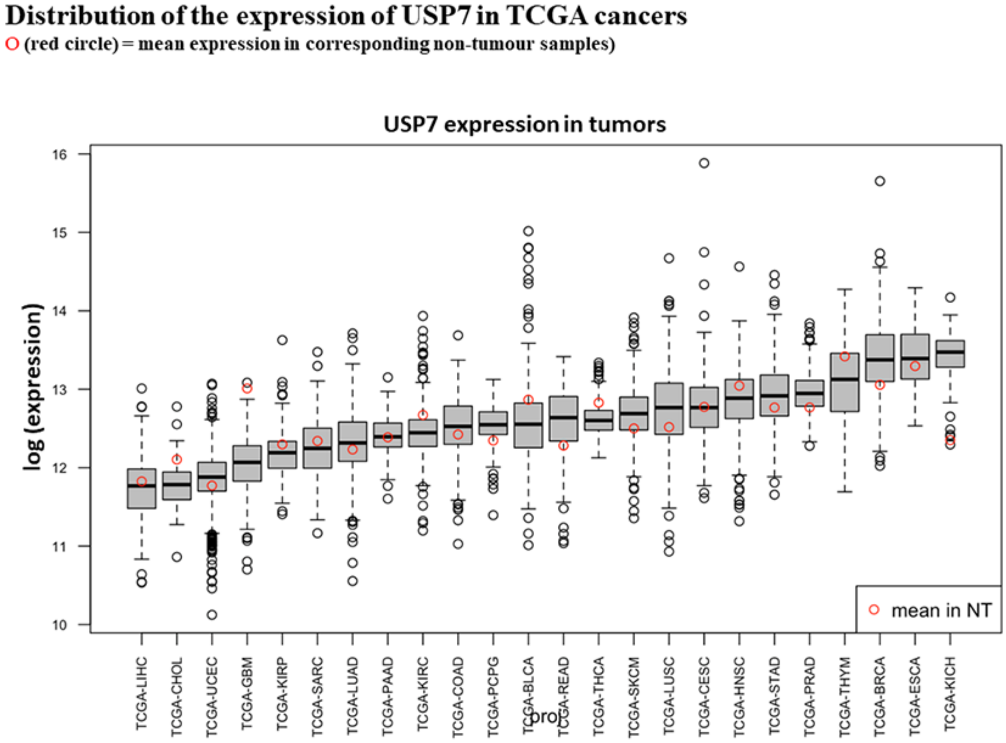
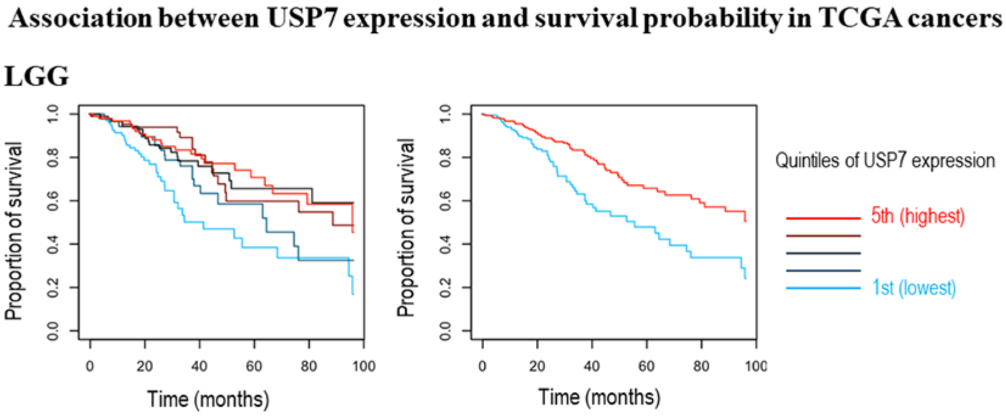


Figure S10. Survival plots representing the association between USP7 expression and survival probability in TCGA-LGG cancer. The y-axis represents the proportion of survival and the x-axis represents survival time (months). USP7, ubiquitin-specific-processing protease 7. For the list of TCGA cancer types analyzed and their abbreviations, please see Table SI.



Association between USP7 expression and survival probability in TCGA cancers

Figure S11. TIP60 is downregulated in cervical cancer. Differential mRNA expression levels of the *TIP60* gene were analyzed in 28 cervical cancer tissues and 24 normal squamous epithelial tissues, with the help of Affymetrix U133A oligonucleotide microarray. A Student's t-test was used to statistically analyze *TIP60* gene expression (**P<0.01). TIP60, Tat interactive protein, 60 kDa.

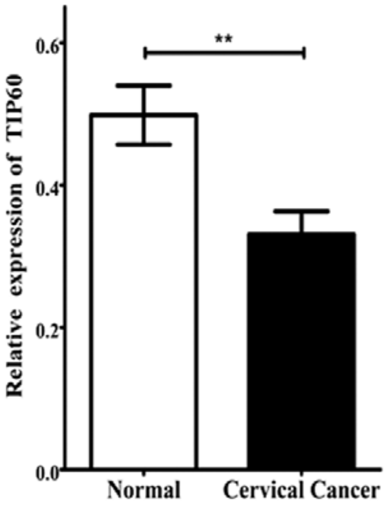


Table SI. List of TCGA cancer types analyzed and their abbreviations.

Abbreviation	No. of samples	Study name
TCGA-ACC	80	Adrenocortical carcinoma
TCGA-BLCA	439	Bladder urothelial carcinoma
TCGA-BRCA	1,217	Breast invasive carcinoma
TCGA-CESC	312	Cervical squamous cell carcinoma and endocervical adenocarcinoma
TCGA-CHOL	45	Cholangiocarcinoma
TCGA-COAD	560	Colon adenocarcinoma
TCGA-DLBC	48	Lymphoid neoplasm diffuse Large B-cell lymphoma
TCGA-ESCA	204	Esophageal carcinoma
TCGA-GBM	471	Glioblastoma multiforme
TCGA-HNSC	604	Head and neck squamous cell carcinoma
TCGA-KICH	91	Kidney chromophobe
TCGA-KIRC	946	Kidney renal clear cell carcinoma
TCGA-KIRP	352	Kidney renal papillary cell carcinoma
TCGA-LAML	197	Acute myeloid leukemia
TCGA-LGG	534	Brain lower grade glioma
TCGA-LIHC	439	Liver hepatocellular carcinoma
TCGA-LUAD	714	Lung adenocarcinoma
TCGA-LUSC	622	Lung squamous cell carcinoma
TCGA-MESO	87	Mesothelioma
TCGA-OV	624	Ovarian serous cystadenocarcinoma
TCGA-PAAD	195	Pancreatic adenocarcinoma
TCGA-PCPG	187	Pheochromocytoma and paraganglioma
TCGA-PRAD	570	Prostate adenocarcinoma
TCGA-READ	814	Rectum adenocarcinoma
TCGA-SARC	271	Sarcoma
TCGA-SKCM	475	Skin cutaneous melanoma
TCGA-STAD	511	Stomach adenocarcinoma
TCGA-TGCT	156	Testicular germ cell tumors
TCGA-THCA	580	Thyroid carcinoma
TCGA-THYM	126	Thymoma
TCGA-UCEC	599	Uterine corpus endometrial carcinoma
TCGA-UCS	57	Uterine carcinosarcoma
TCGA-UVM	80	Uveal melanoma