SUPPLEMENTARY METHODS

In vitro coculture of macrophages with prostate cancer cells

5000 RAW264.7 cells in 500 µL cell culture medium/well were plated in 24-well cell culture plates, and 5,000 RM-1-BM SPOP-variant cells in 500 µL cell culture medium were plated. For monoculture controls, the same number of both cell types in 1,000 µL cell culture medium/well were directly plated in 24-well plates. The plates were incubated in 37°C CO2 incubator for 24 hrs before treatment with the indicated drug for 48 hrs, followed by MTS assay to read OD490nm values as previously reported. For THP-1 and C4-2b (VC, SPOPF102C, and SPOPF133V) co-culture, 1 X 10^4 THP-1 cells in 500 µL cell culture medium/well were first plated in 24-well cell culture plates (Cat# 08-771, ThermoFisher, Waltham, MA) in the presence of 150 nM PMA (phorbol-12-myristate-13-acetate, Cat# P8139, MilliporeSigma, Burlington, MA) and incubated in 37°C CO_2 incubator for 24 hrs (1). The media was replaced with 500 µL cell culture medium without PMA/well the next day, and incubated with 5,000 C4-2b-VC /or SPOPmuts cells plated in with 0.4 µm TransWell inserts provided with the plate for 48 hours as above-mentioned with the monocultures. The MTS cell proliferation was presented as the OD 490 nm values of all drug treatments normalized to those of vehicle (DMSO), then to EV, and finally coculture to monoculture. To collect cells for total RNA extraction, 0.4 µm 6-well TransWell cell culture inserts (Cat# 140640, ThermoFisher) were used. RAW264.7 cells in 1.5 mL cell culture medium/well and RM-1-BM SPOP-variant cells in 1.0 mL cell culture medium/well were started with 2 X 10^5 cells/well, and THP-1 cells were started with 3.0 X 10^5 cells/well and co-cultured with 2.0 X 10^5 cells/well C4-2b SPOP-variant cells.

Mammalian protein expression vector plasmid constructs and methods to generate of lentiviral expression vectors for SPOP and SPOP mutant utilizing PCR-based, site-directed mutagenesis and Gate-way cloning®

Venus1-tagged STING1 (STING1-V1) was a gift from Eric Schirmer (Addgene plasmid #124262; http://n2t.net/addgene:124262; RRID: Addgene_124262). Flag-tagged STING1 (pCMV-TMEM173-Flag, Cat# HG29810-CF) was purchased from Sino Biological, Inc. (Sino Biological Inc., Wayne, PA). Human RBX1 mammalian expression vector pCDNA3-myc3-ROC1 was a gift from Yue Xiong (Addgene plasmid #20717; http://n2t.net/addgene:20717; RRID:Addgene_20717) (2). Human Cullin 3 mammalian expression vector pcDNA3-myc-CUL3 was a gift from Yue Xiong (Addgene plasmid #19893; http://n2t.net/addgene:19893; RRID:Addgene_19893) (3). His-tagged human ubiquitin mammalian expression vector PCI-His-hUbi was a gift from Astar Winoto (Addgene plasmid #31815; http://n2t.net/addgene:31815; RRID:Addgene_31815) (4). These plasmid constructs were propagandized in bacterial as instructed by Addgene product insert, sequencing confirmed, transfected into mammalian cell line 293T cells for overexpression, coexpression, co-IP and in vivo ubiquitination assay experiments.

Dox-inducible SPOP expression pInducer-SPOP lentiviral vectors (pInducer-EV, pInducer-SPOPwt, pInducer-SPOPF102C, pInducer-SPOPF133V), pInducer-EV control vector, constitutive SPOP expression pLenti-SPOP lentiviral vectors (pLenti-SPOPwt, pLenti-SPOPF102C, and pLenti-SPOPF133V) and pLenti-EV control vector were generated utilizing lentiviral vector pInducer 20 (a gift from Stephen Elledge, Addgene plasmid #44012; http://n2t.net/addgene:44012; RRID:Addgene_44012) (5) and lentiviral vector pLenti CMV Puro

DEST (W118-1) (a gift from Eric Campeau & Paul Kaufman, Addgene plasmid #17452; http://n2t.net/addgene:17452; RRID:Addgene_17452) (6).

To generate pcDNA3.1-HA-SPOPwt, Ha-tagged, full-length SPOP mRNA coding sequence was amplified by PCR [using pcDNA3.1-2xFlag-SPOPwt (described in our previous publication, (7) as the template], double-digested with restriction enzymes BamHI (Cat# R3136, New England Biolabs, Ipswich, MA) and NotI (Cat# R3189, New England Biolabs), purified, and inserted into pcDNA3.1 vector digested by the same pair of restriction enzymes. The PCR primers used for this purpose were: Forward-5'-CTC**GGATCC** (*BamHI*) AGTACCCTTCACCATGGCTTACCCA TACGATGTTCCAGATTACGCTATGTCAAGGGTTCCAAGTCCTCCA-3' and Reverse-5'-CGGGTTTAAACGGGCCCTCTAGAC-3'. To generate pcDNA3.1-HA-SPOPF102C and pcDNA3.1-HA-SPOPF133V vectors, site-directed mutagenesis (SDM) protocol and a Q5® Site-Directed Mutagenesis Kit (Cat# E0554S, New England Biolabs, MA) were used following the kit manual, with pcDNA3.1-HA-SPOPwt vector as the mutagenesis PCR template. The primer pairs used for mutagenesis were Forward-5'- GTCCAAAGAGTGAAGTTCGGGCAAAA*TGC* (**F→C**) AAATTCTCCATCCTGAATGCCAAGGGAGAAG-3' and Reverse-5'-GCATTTTGCCCGAACT TCACTCTTTGGACAG-3' for SPOPF102C; and Forward-5'- GTGCAAGGCAAAGACTGGGG A*GTC* (**F→V**) AAGAAATTCATCCGTAGAGATTTTCTTTT-GGATGAGG-3' and Reverse-5'-GAATTTCTTGACTCCCCAGTCTTTGCCTTG-3' for SPOPF133V. The resultant plasmid constructs were confirmed by DNA sequencing.

To generate pENTR-HA-SPOPwt, pENTR-HA-SPOPF102C, and pENTR-HA-SPOPF133V Gateway entry clone vectors, SPOPwt, SPOPF102C, and SPOPF133V coding sequences (respectively) were amplified by PCR (using pcDNA3.1-HA-SPOPwt, pcDNA3.1-HA-SPOPF102C, and pcDNA3.1-HA-SPOPF133V vectors, respectively, as templateS) and inserted into pENTR/D-TOP vector using a pENTR™/D-TOPO™ Cloning Kit, following the instructions of the kit manual (Cat# K240020, ThermoFisher). The primers used for PCR amplification were Forward-5'- CACCATGGCTTACCCATACGATG-3' and Reverse-5'-CTTTCCGCCTCAGAA GCCATAGAG-3'. In addition, we generated pENTR-RND entry vectors with the insertion of a synthetic, short noncoding random dsDNA sequence (96bp, Forward-5'- CACCGCATC GATTGATTCAGCGGACGGTGTTGTTTTAGGTCATAGATTCGGCACATTTCCCTTGTAGGTG TGAAATCACTTAGCTTCGCGCCGTAG-3' and Reverse-5'- CTACGGCGCGAAGCTAAGTGA TTTCACACCTACAAGGGAAATGTGCCGAATCTATGACCTAAAACAACACCGTCCGCTGAAT CAATCGATGCGGTG-3') as the entry vectors for Gateway cloning of EV control. The resultant pENTR-SPOP plasmid constructs and pENTR-RND vector were confirmed by DNA sequencing and used for Gateway cloning procedures to generate Dox-inducible expression lentiviral vectors (pInducer 20) or constitutive expression lentiviral vectors (pLenti CMV Puro DEST) for SPOPs.

To generate lentiviral vectors for SPOPwt, SPOPF102C, or SPOPF133V expression, Gateway® cloning protocol and Gateway™ LR Clonase™ II Enzyme mix (Cat# 11791020, ThermoFisher) were used following the product user instructions. pInducer 20 was used to generate Dox-inducible SPOPs' (SPOPwt, SPOPF102C, or SPOPF133V) expression lentiviral vector and pLenti CMV Puro DEST (W118-1) was used to generate constitutive expression lentiviral vector for SPOPs (SPOPwt, SPOPF102C, or SPOPF133V). Following a similar procedure, pENTR-RND was used to generate pInducer-EV and pLenti-EV. The resultant expression vectors, Dox-inducible SPOP expression pInducer-SPOP lentiviral vectors (pInducer-EV, pInducer-SPOPwt, pInducer-SPOPF102C, pInducer-SPOPF133V), pInducer-EV control vector) and constitutive

SPOP expression pLenti-SPOP lentiviral vectors (pLenti-SPOPwt, pLenti-SPOPF102C, and pLenti-SPOPF133V) and pLenti-EV control vector) were all confirmed by DNA sequencing.

Immunostaining and immunofluorescence analysis of tumor tissues

4 µm sized paraffin tissue sections were de-paraffinized with Xylene, rehydrated through graded alcohols and subjected to antigen retrieval using 10 mM sodium citrate buffer (pH 6.0) in the microwave oven, and endogenous peroxidase activity was quenched with 3% H_2O_2 for 10 minutes in the dark. The sections were washed with TBS/T (**T**ris-**B**uffered **S**aline w/ 0.1% Tween-20) and then blocked with Protein Block (Cat# X0909, Dako, Santa Clara, CA) for 1 hr at room temperature. Slides were incubated with the respective primary antibody diluted with Antibody Diluent (Cat# S0809, Dako) (1:100 for both antibodies) in a wet box at 4°C overnight. Slides were then washed for 10 min in TBST and incubated for 1 hour with ImmPRESS®-HRP Horse Anti-Rabbit IgG Polymer Reagent (Cat# MP-7401, Vector Laboratories, Newark, CA). After washing, slides were incubated with DAB (3,3'-diaminobenzidine tetrahydrochloride) (Cat# K3468, Dako) 1 min for anti-phospho-Ser366-STING antibody and 5 min for anti-phospho-Ser754-STAT3 antibody, and immediately washed distilled water. Lastly slides were counter stained with Gill III hematoxylin solution (Cat# 105174, MilliporeSigma) and washed under tap water for color development. Slides were eventually mounted with Permount Mounting Media (Cat# SP15-500, ThermoFisher) and were then observed and images taken with a light microscope (Nikon Eclipse 90i).

The antibody specific DAB staining intensity was quantitated by using ImageJ from 5 random hot areas in one representative well white-balanced image of, at least, three different fields of one tumor sample. Two to three tumors from each group were analyzed. The DAB specific staining intensity was calculated with the following formula: DAB specific staining intensity=Log (max intensity/mean intensity) where max intensity = 255 for 8-bit images.

For immunofluorescence analysis, paraffin embedded tissue sections were de-paraffinized, dehydrated and subjected to antigen retrieval as mentioned above. The sections were washed with PBS and then permeabilized with PBS with 0.2% Triton X-100 (Cat# X-100, MilliporeSigma, Burlington, MA, permeabilization buffer) for 20 min, and then blocked with 5% BSA (**B**ovine **S**erum **A**lbumin, Cat# A9647, MilliporeSigma) in the permeabilization buffer for 1 hr at room temperature. Slides were then incubated with rabbit monoclonal antibody anti-phospho-histone H2A.X (Ser139) (ɣ-H2AX) (1:400, Cat# 9718, Cell Signaling Technology), rabbit monoclonal anti-cleaved caspase 7 antibody (1:400 dilution, Cat# 8438, Cell Signaling Technology), rabbit polyclonal anti-IFN-β antibody (1:100 dilution, Cat# NPB1-77288, Novus Biologicals, Centennial, CO), mouse monoclonal anti-human PARP1 antibody (1:100 dilution, Cat# sc-8007, Santa Cruz Biotechnology) in 1% BSA in a wet box at 4°C overnight. Slides were subsequently washed for 10 min with the permeabilization buffer, three times, and incubated for 1 hour at room temperature, protected from light with secondary antibody goat-anti-rabbit IgG (H+L) cross-absorbed antibody Alexa Fluor ™594 (1:500, Cat# A-11012, ThermoFisher), goat-anti-rabbit IgG (H+L) cross-absorbed antibody Alexa Fluor ™488 (1:500 dilution, Cat# A-11008, ThermoFisher) or goat anti-mouse IgG (H+L) cross-absorbed secondary antibody, Alexa Fluor™ 647 (1:1,000 dilution, Cat# A-20990, ThermoFisher) in 1% BSA. After washing, slides were mounted with Prolong antifade with DAPI (Cat#P36931, ThermoFisher). Immunofluorescence was visualized and images taken under Leica SP8 fluorescent microscope.

Double immunofluorescence of PARP1 and cleaved caspase 3 was performed using mouse monoclonal anti-human PARP1 antibody (1:100 dilution, Cat# sc-8007, Santa Cruz Biotechnology) and rabbit monoclonal anti-cleaved casepase 3 antibody (1:400 dilution, Cat#

9664, Cell Signaling Technology), goat anti-mouse IgG (H+L) cross-absorbed secondary antibody, Alexa Fluor™ 594 (Cat# A-11012, ThermoFisher) and goat-anti-rabbit IgG (H+L) cross-absorbed antibody Alexa Fluor ™488 (Cat# A-11008, ThermoFisher), both at 1:500 were used. Slides from representative tumor from each group was used and one representative image from, at least, five different fields with tumor cells from one slide was presented. Total number of cells were assessed with ImageJ. Numbers of cells with clear cleaved caspase-3, PARP-1 cytoplasmic accumulation, and both were counted manually.

LC-MS/MS proteomic profiling analysis

Dox-inducible SPOPwt (SPOPwt and EV) and SPOPmut (F102C and F133V) C4-2b prostate cancer models were labeled with 13C6 Lys (Cat #CNLM-2247, Cambridge Isotope Laboratories) in RPMI1640 containing 10% dialyzed FBS and 1% penicillin/streptomycin cocktail (Gibco). SILAC labeling was used to discriminate FBS-derived proteins from cell proteins. Briefly, for proteomic analysis of whole-cell lysates, 2×10^7 cells were lysed in 1 mL PBS (**P**hosphate-**B**uffered **S**aline)containing octyl-glucoside (1% w/v) and protease inhibitors (cOmplete, Roche Diagnostics), followed by sonication and centrifugation at 20,000×*g* with collection of the supernatant and 0.22-μm filtration. Whole-cell extract (2 mg) proteins were reduced in DTT and alkylated with acrylamide before fractionation with RP-HPLC. A total of 84 fractions were collected. Mobile phase A: H2O:ACN (95:5, v/v) with 0.1% of TFA. Mobile phase B: ACN:H2O [95:5] with 0.1% of TFA. Collected fractions were lyophilized, followed by in-solution trypsin digestion (ThermoFisher).

Based on the chromatogram profile, 84 fractions were pooled into 24 fractions for LC-MS/MS analysis per cell line. In total, 2,688 fractions were analyzed by RPLC-MS/MS using a nanoflow LC system (EASYnano HPLC system, ThermoFisher) coupled online with an LTQ Orbitrap ELITE mass spectrometer (ThermoFisher). Separations were performed using 75 μm id × 360 μm od × 25-cm-long fused-silica capillary column (Column Technology) slurry packed with 3 μm, 100 A° pore size C18 silica-bonded stationary phase. Following injection of ~2 μg of protein digest onto a C18 trap column (Waters, 180 μm id × 20 mm), peptides were eluted using a linear gradient of 0.35% mobile phase B (0.1 formic acid in ACN) per minute for 90 min, then to 95% B for an additional 10 min, all at a constant flow rate of 300 nL/min. Eluted peptides were analyzed by LTQ Orbitrap ELITE in data-dependent acquisition mode. Each full MS scan (m/z 400–1800) was followed by 20 MS/MS scans (CID normalized collision energy of 35%). Acquisition of each full mass spectrum was followed by the acquisition of MS/MS spectra for the 20 most intense +2, +3, or +4 ions within a duty cycle, dynamic exclusion was enabled to minimize redundant selection of peptides previously selected for MS/MS analysis. Parameters for MS1 were 60,000 for resolution, 1×10^6 for automatic gain control target, and 150 ms for maximum injection time. MS/MS was done by CID fragmentation with 3×10^4 for automatic gain control, 10 ms for maximum injection time, 35 for normalized collision energy, 2.0 m/z for isolation width, 0.25 for activation *Q* value, and 10 ms for activation time.

MS/MS spectra were searched against the Uniprot database (Human and Bovine, January 2017) using the X!Tandem search engine through the Trans-Proteomic Pipeline (TPP 4.8) and processed with the Peptide and Protein Prophet. Trypsin was specified as protein cleavage site, with the possibility of two missed cleavages allowed. For the modifications, one fixed modification of propionamide (71.037114) at cysteine and two variable modifications, oxidation at methionine (15.9949 Da) and SILAC 13C6 at lysine (6.0201 Da), were chosen. Addition of SILAC was used strictly to discriminate human protein from bovine protein and was not intended to perform relative quantitation of Heavy versus Light ratios. The mass error allowed was 10 ppm for parent monoisotopic and 0.5 Da for MS2 fragment monoisotopic ions. The searched result was filtered

with FDR = 0.01. Ingenuity Pathway Analyses of these 81 proteins revealed enriched representation of an NF-κB–centric protein network.

Gene expression analysis

The raw sequence reads from RNA samples of RM-1-BM-SPOPF133V /or -EV were aligned to the Mouse genome (build - GRCm38), with Star transcriptome alignment software (8). HTseq software was used to summarize the expression counts per gene from alignment data (9). Pre-processed RNAseq and WES data from TCGA, Beltran and Robinson datasets was utilized in this analysis (24,13-16).Normalization of RNA-seq counts and differential expression analysis was performed on the read counts with the R package DESeq2 (10) for all the datasets utilized. P values obtained after multiple tests were adjusted for using the Benjamini-Hochberg method (11). Hierarchical clustering (Pearson distance and Ward linkage) and principal component analyses were used for unsupervised expression investigation.

Functional evaluation of the transcriptomic data for enrichment of was performed using a customized gene set collection defined in relevant existing literature. For this purpose, a STING-NF-κB signaling pathway (12) and other related gene sets comprising a comprehensive list of 259 signature genes of canonical (cGAS-STING) and non-canonical-STING (NC-STING) innate immune signaling pathway (18 ,19-23) were used by reviewing the data in relevant publications. Using these pre-defined gene sets, GSEA analysis was performed in annotated datasets of CRPC patient tumors (13-16) based on the test statistic obtained from differential expression between SPOPmut and SPOPwt cohorts (17). Significant differentially regulated genes (DRGs) associated with SPOPmut cohorts among the prostate cancer patients in Beltran dataset (14,15) were defined by FDR < 10% and log2FoldChange > 0.5. These significant upregulated DRGs, as “NC-STING signature” were evaluated by examining it in SPOPmut cohort among the primary, hormone-naïve patients from TCGA (24). NC-STING Score was computed for the TCGA samples as z-score of gene expression of NC-STING signature.

Far western blotting analysis to detect direct protein–protein interaction of SPOP and STING protein in vitro

Using purified STING protein (cat.#81182, Active Motif, Carlsbad, CA) and cell lysates from 293T cells overexpressing SPOPwt or its substrate binding-defect mutants, SPOPF102C and SPOPF133V, far western blotting analysis was conducted to detect and confirm the direct protein-protein interaction of STING protein and SPOP in vitro following a standard protocol (25, 26, 27) with modifications. Briefly, SPOPwt, SPOPF102C and SPOPF133V overexpressed 293T cell lysates were loaded and separated by SDS-PAGE and transferred to PVDF membrane following a standard western blotting protocol. For far western blotting assay, the membrane was blocked with blocking buffer (1% BSA in PBS/T buffer) and incubated with purified STING protein, diluted in blocking buffer overnight. Thereafter, the membrane was washed and blotted with anti-STING antibody (Cat. #504945, Cell Signaling Technology). Finally, the membrane was incubated with HRP-linked anti-rabbit secondary antibody and then, the blot signals were visualized by incubating the membrane with SuperSignal West chemiluminescence substrate (ThermoFisher) and imaged on a VersaDoc™ MP image system (BioRad, Hercules, CA) as we did in a standard immune blot assay in Methods and Materials. Two sets of similar loadings separated by SDS-PAGE and transferred onto the same PVDF membrane previously used for far western blot were cut out and blotted with anti-STING or anti-HA (to detect HA-tagged SPOPwt, SPOPF102C and SPOPF133V) following standard immune blot protocols, without incubation of purified STING protein, as controls to indicate the background (negative STING interaction control) and as a

positive SPOP loading control. The images from the membranes of sample loading set probed by anti-STING (without purified STING protein incubation), anti-STING (with purified STING protein incubation) and anti-HA-SPOPs were arrayed [according to the pre-stained protein molecular weight markers (Cat.# M00624, GenScript Biotech., Piscataway, NJ) loaded between each similar loading sample set] to compare and identify blot signals specifically recognized by anti-STING at the same molecular weight of SPOP when purified STING protein was presented to the membrane incubation.

STAT3 transcription factor binding site prediction in selective gene promoters

Published STAT3 ChIP-seq datasets were downloaded and analyzed utilizing Integrative Genomics Viewer (IGV) (28-34). A public database for aggregated analysis of STAT3 ChIP-seq data ENCODE Transcription Factor Targets dataset (https://maayanlab.cloud/Harmonizome/gene_set/STAT3/ENCODE+Transcription+Factor+Targets) was provided to predict STAT3 targets (35). The genomic DNA sequences of the STAT3 ChIP-seq enriched genomic regions that reside within the promoters of selective genes were extracted, examined and compared to identify the consensus STAT3 binding DNA sequences utilizing JASPAR2022 database (https://jaspar.genereg.net/search?q=STAT3). Comparative analysis of these data predicted recruitment of STAT3 to promoter regions of HMGA1, HMGB1 and HMGB3 genes, suggesting transcriptional regulation of these genes in cells of different origins (32, 36, 37).

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