Supplementary Methods

Cell Culture Condition

All tumor cell lines and their genetically modified lines were cultured in RPMI-1640 or DMEM medium with 10% heated-inactivated FBS and 100 μg/ml of Normocin (InvivoGen). MC38/gp100-Cas9 cells (MC38/GC) were maintained in complete RPMI-1640 media with 1μg/ml of blasticidin (Invitrogen). All cell lines were authenticated by short tandem repeat fingerprinting or the expression of tagged markers used for genetic modification. The MycoAlert kit (Lonza) was used to routinely monitor for mycoplasma contamination of cultured cells. The maximum length of time of *in vitro* cell culture between thawing and use in the described experiments was two weeks.

Generation of tumor-reactive T cells

To obtain T cells which can recognize murine MC38/gp100 tumor cells, splenocytes were isolated from Pmel-1 mice and cultured in complete RPMI 1640 media (10% FBS, 20mM HEPES, 1mM sodium pyruvate, 0.05mM 2-mercaptoethanol, 2mM L-glutamine and 50U/ml streptomycin and penicillin) supplied with 300 U/ml rhIL-2 interleukin-2 (Prometheus Laboratories) in presence of 0.3μg/ml anti-mouse CD3 (BD Biosciences, San Jose, CA) for 24 h. After stimulation, cells were maintained in the culture medium with 300 IU/ml IL-2 for 6 days. Luciferase-expressing Pmel-1 T cells used for *in vivo* studies were generated as described previously.[1]

Given that H2023 is a human lung cancer cell line expressing both MAGE-B2 and HLA-A0201, we generated T cells which can recognize HLA-A2 restricted MAGE-B2 as previously described.[2] Briefly, the retroviral vector encoding a T cell receptor (TCR) which recognizes and

specifically binds the HLA-A2 restricted MAGE-B2 epitope (GVYDGEEHSV) was previously constructed.[3 4] To obtain and expand TCR-T cells specifically recognizing H2023, peripheral blood mononuclear cells (PBMCs) were collected by leukapheresis from HLA-A2 expressing healthy donors. PBMCs were first activated with anti-CD3 mAb (OKT3; Ortho Tech) for 24 hours and followed by a retroviral transduction to express MAGE-B2 specific TCR. The transduced cells were expanded in AIM V medium (Gibco) containing 5% heat-inactivated human AB Serum (Valley Biomedical), 2 mM GlutaMax (Gibco), and 300 U/mL IL-2 for additional 7-10 days. The expanded T cells were harvested and used for cryopreserved for *in vitro* experiments.

Establishment of genetically modified tumor cell lines

Lentiviral based gene delivery was used to genetically perturb the expression of gene-of-interest in tumor cells. To generate viral supernatants, HEK293T cells were seeded 12 hours prior to transfection and transfected with the lentiviral vectors encoding either gRNAs, along with lentiviral packaging plasmids, pCMV-VSV-G (Addgene #8454) and psPAX2 (Addgene #12260) by the jetPRIME® transfection reagent (Polyplus-transfection) according to the manufacturer's protocol. The viral supernatant was collected 48 hours post transfection and filtered by 0.45nm PVDF Syringe Filter Unit (Millipore) to remove cell debris. Lentivirus was added directly to cultured cell lines together with 8μg/ml hexadimethrine bromide (Sigma-Aldrich). 48 hours after transduction, cells were cultured with growth medium in present of appropriate antibiotics to select transduced tumor cells. The lentiviral vector, lentiCas9-Blast (Addgene #52962), encoding the open reading frame of *Cas-9*, was used to exogenously express cas-9 in MC38/gp100 tumor cells.[5] The lentiviral vector, pKLV2-U6gRNA5(BbsI)-PGKpuro2ABFP-W (Addgene #67974), was used to construct vectors encoding murine *Prmt1* and *Ripk1* specific gRNAs as previously

described.[5 6] The lentiviral vector, lentiCRISPR v2 (Addgene #52961), was used to construct vectors encoding human *PRMT1* and *RIPK1* specific gRNAs. The target sequences of gRNAs for human/murine *PRMT1* or *RIPK1* were list in the online supplementary table 2. In addition, two vectors encoding non-targetable gRNAs were also constructed and used to generate the control cell lines.

Bioinformatics analyses

For the Next Generation Sequencing (NGS) results from the genome-wide gRNA screens, the sequencing reads were mapped to the Mouse V2 CRISPR library using bowtie (1.2.2) with parameters "--best --strata -a --norc -m 1 -5 20 -3 30 -S".[7] Samtools (1.9) was used to calculate the read count of r each sgRNA.[8] MAGeCK (0.5.7) was used with parameters "--gene-lfc-method secondbest -n ET03 --normcounts-to-file --additional-rra-parameters '--permutation 10000'" to identify the genes that showed a differential selection (fold-change>2 and $p<0.05$) between the control and T cell treated groups, as described previously.[9]

The gene expression values and clinical information were obtained from the Skin Cutaneous Melanoma (SKCM) TCGA dataset via the UCSC Toil RNAseq Recompute Compendium. [10] The gene-level Transcripts Per Kilobase Million (TPM) values was log2-transformed with pseudo-count 1 for further analysis. The Mann-Whitney U test was used for the differential expression analysis. The tumor purity was calculated using the ESTIMATE method[11], as described previously.[12 13] The lymphocyte infiltration score (LScore) was obtained from the clinical annotation of the SKCM cohort. The expression level of a candidate gene was compared between LScore-low (0-3) and -high (4-6) group, using the Mann-Whitney U test. The CYT Score was calculated as the geometric mean of the TPM values of *GZMA* and *PRF1*.

For the analysis of RNA-seq data generated in *Prmt1*-Knockout (KO), *Ripk1*-KO, and negative control sgRNA-treated MC38/gp100 cell lines, the raw sequencing reads were mapped to mouse genome (mm10) and transcriptome (GENECODE vM14) using HiSAT2 2.1.0[14] with parameters "--strandness R". The gene-level read counts were calculated using preDE.py from StringTie 1.3.0 [15] based on mouse GENECODE vM14 transcriptome annotation. The human homologue gene names were obtained from the MGI mouse-human homologue annotation. The normalization and differential gene expression were performed by edgeR [3.24.3].[16] Gene Set Enrichment Analysis (GSEA)[17] was applied to the log-fold change ranked genes to identify the hallmark gene sets curated by MSigDB [18] that showed significant enrichment of over-expressed or under-expressed genes upon *Prmt1/Ripk1* KO. The apoptosis-related genes (GO: 0097190) and cytokine/chemokine genes (GO: 0005125) defined by Gene Ontology[19] were selected to compare the changes in their mRNA expression levels upon Prmt1/Ripk1 KO.

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