Figure S1

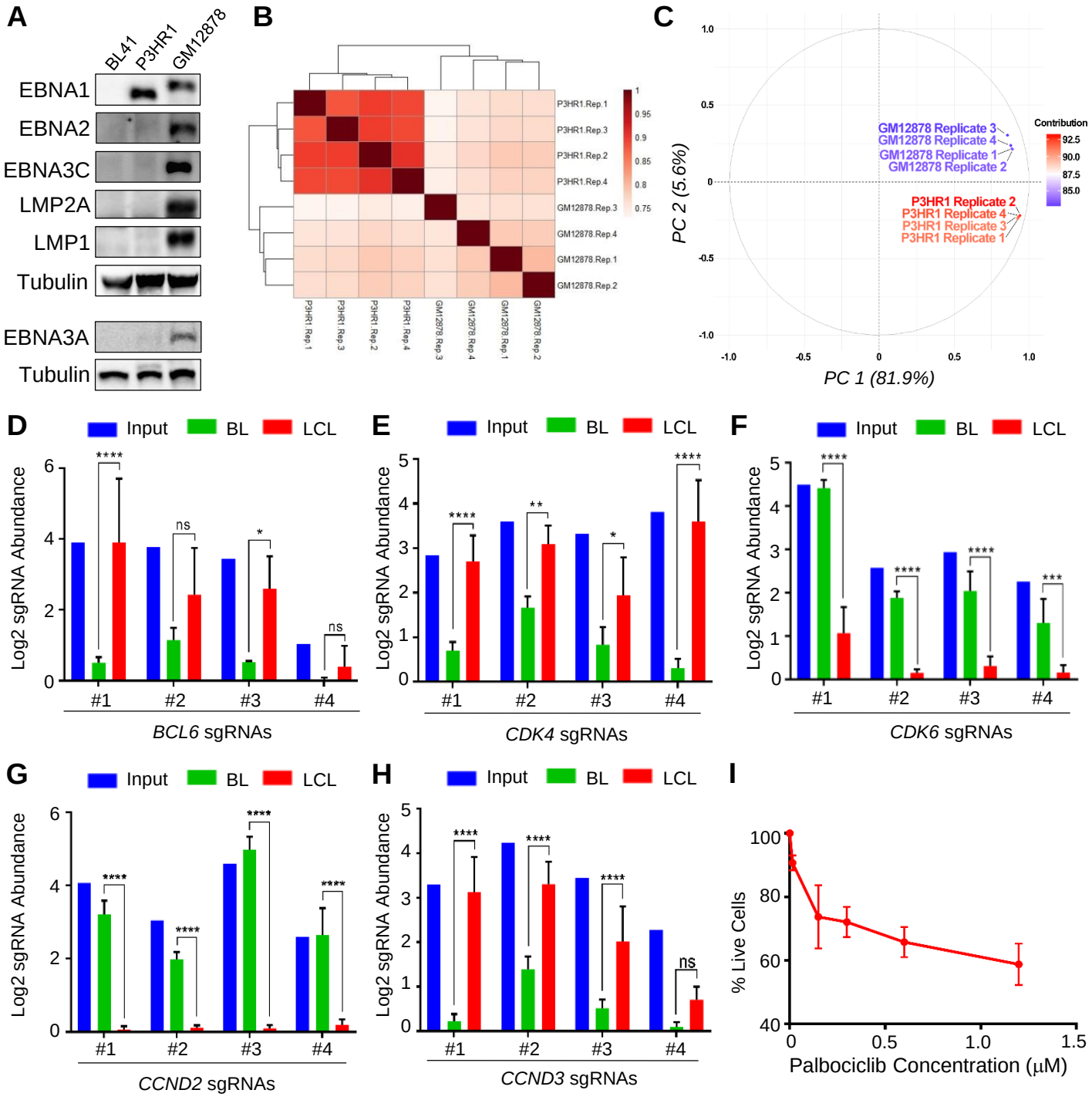

Figure S1. Comparison of GM12878 and P3HR1 Growth and Survival Screens, Related to Figure 1 and 2. (A) Immunoblot analysis of EBNA and LMP expression in BL41(EBV-negative control), P3HR1 and GM12878 whole cell lysates. (B) Heatmap analysis of correlation between GM12878 and P3HR1 CRISPR screen quadruplicates. (C) Principal component analysis of variance between GM12878 and P3HR1 quadruplicate screens. (D-H) Log2 abundances of sgRNAs targeting (D) *BCL6*, (E) *CDK4*, (F) *CDK6*, (G) *CCND2*, or (H) *CCND3* in the Avana library input (Day 0, blue), P3HR1 (Day 21, green) or GM12878 (Day 21, red). Mean and standard deviations (S.D.) of quadruplicate values are shown; ***, p<0.001; ****, p<0.0001. (I) Dose-response analysis of GM12878 treated with the CDK4/6 antagonist palbociclib for 48 hours. Mean and S.D. of triplicate experiments are shown.

Figure S2

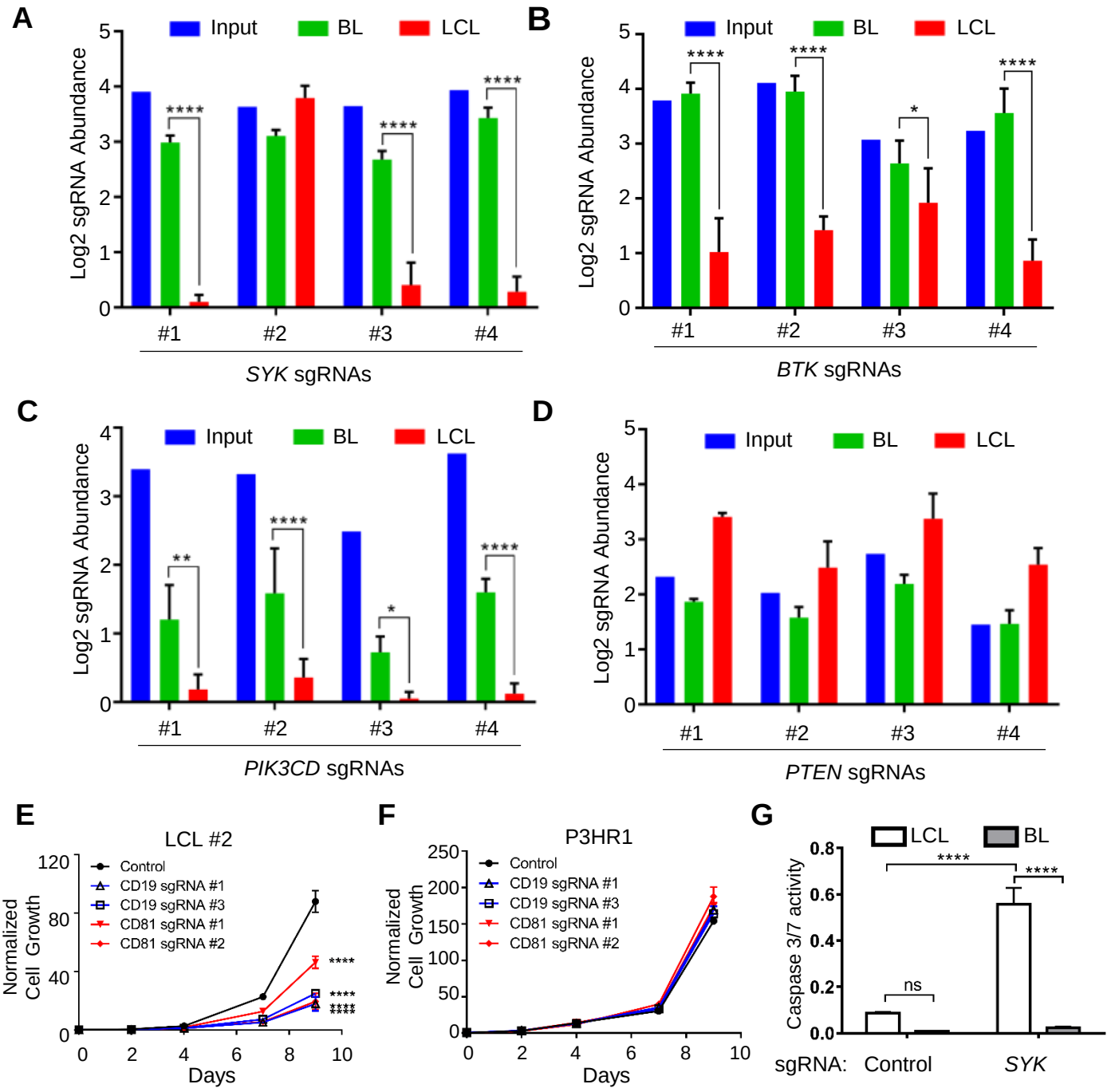

Figure S2. CRISPR/Cas9 Screens Identify EBV LMP2A Pathway Hits, Related to Figure 3. (A-D) Log2 sgRNA abundances for (A) *SYK*, (B) *BTK*, (C) *PIK3CD* (targets the gene encoding the PI3K p110 catalytic subunit delta isoform) and (D) *PTEN* in the Avana library input (Day 0, blue), P3HR1 (Day 21, green) or GM12878 (Day 21, red). Mean and S.D. of quadruplicate values are shown. (E-F) Effects of control, *CD19* and *CD81* sgRNAs on (E) a second LCL versus (F) P3HR1. Data are shown as means of triplicate experiments with S.D. (G) Caspase 3/7 activity in GM12878 (open box) versus P3HR1 (gray box) 5 days following expression of control or *SYK* sgRNA. Means of independent triplicates are shown with S.D. *, P<0.05; ** p<0.01; ****, p<0.0001.

Figure S3

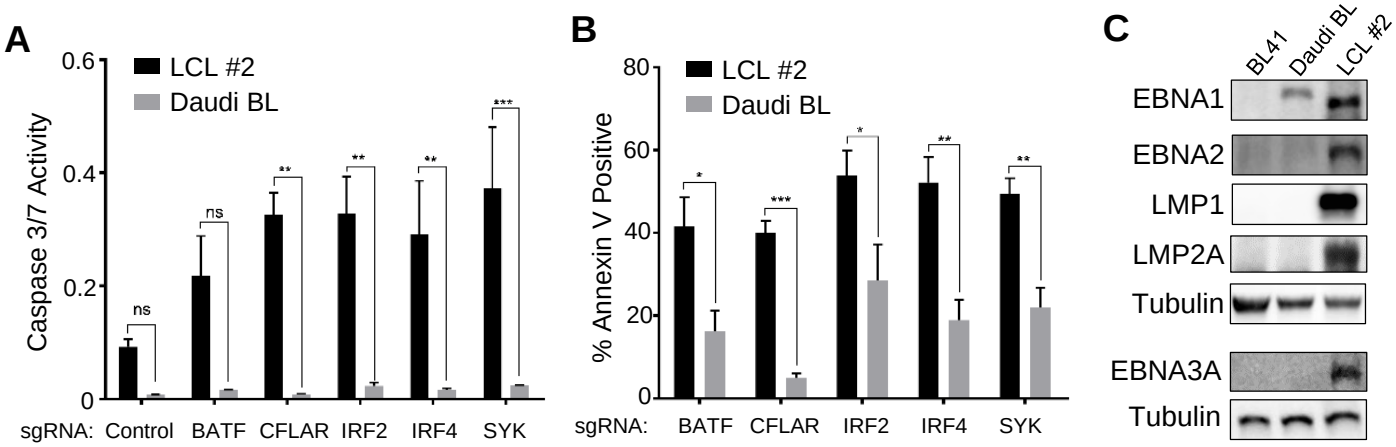

Figure S3. Screen Hit Validation in a Second LCL and BL Pair, Related to Figures 4-7. (A) Caspase 3/7 activity assay in a second LCL (LCL #2) versus the EBV+ Daudi BL cell line, 6 days after transduction with the indicated sgRNAs. (B) % of cell surface Annexin V positive LCL #2 versus Daudi BL cells 6 days after transduction with indicated sgRNAs. All values are normalized to control background values. Means of independent triplicates are shown with S.D. *, $p<0.05$; **, $p<0.01$; ***, $P<0.001$. (C) Immunoblot analysis of EBNA and LMP expression in BL41(EBV-negative control), Daudi and LCL #2 whole cell lysates.

Figure S4

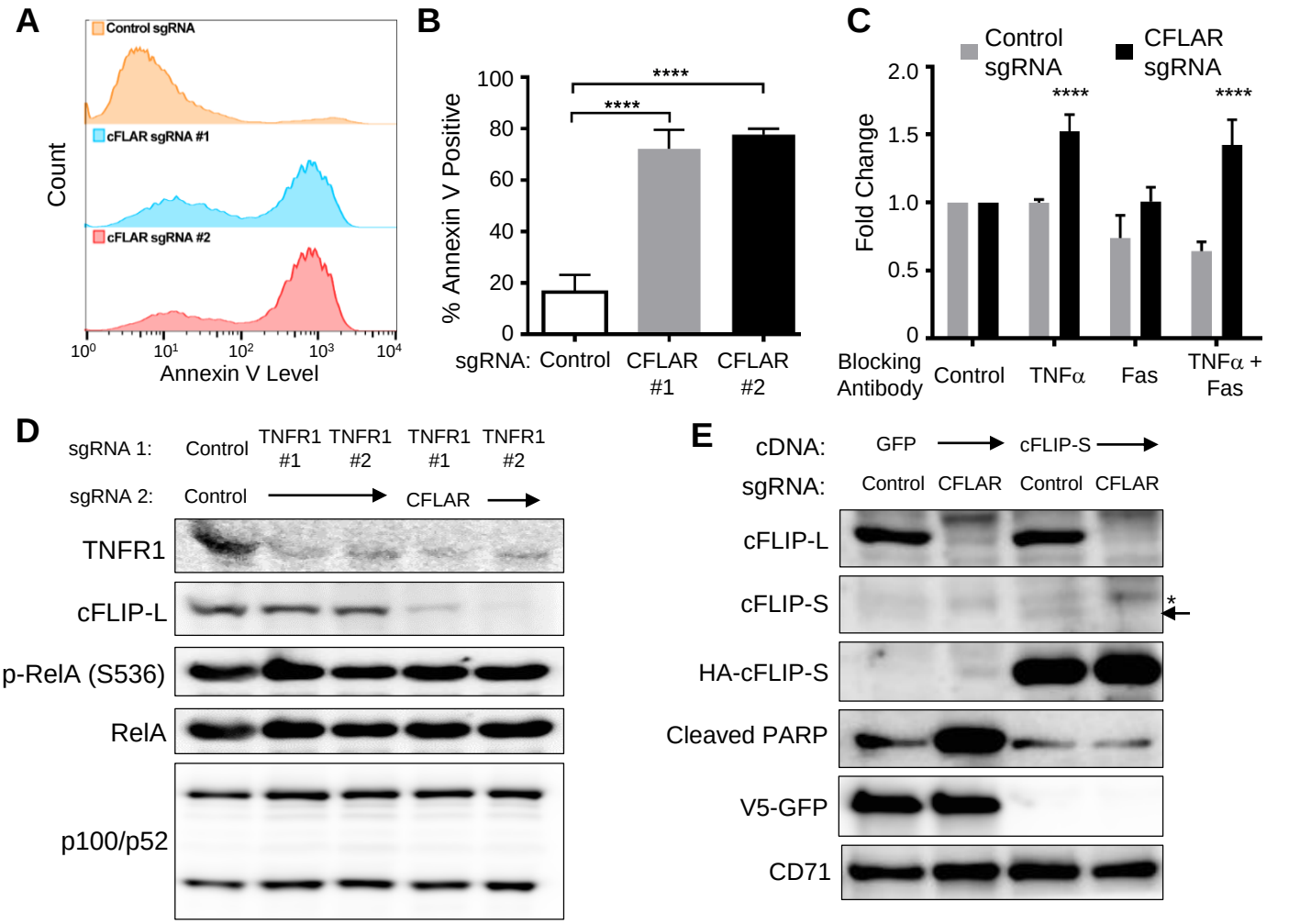

Figure S4. LMP1-induced cFLIP Blocks LCL Apoptosis and Necroptosis, Related to Figure 4. (A) FACS analysis of plasma membrane Annexin V levels in GM12878, 5 days after expression of control or *CFLAR* sgRNAs. (B) Annexin V mean and S.D. values of triplicate experiments, as in (A). (C) GM12878 were transduced with lentivirus expressing control or *CFLAR* sgRNA. 1 day later, blocking antibodies were added and refreshed after 48 hours. 5 days after sgRNA transduction, fold change was calculated as the live cell number ratio of antibody treated to vehicle control treated cells. Data are shown as triplicate mean with S.D. (D) Immunoblot analysis of GM12878 expressing the indicated sgRNAs. Control and TNFRSF1A sgRNA were first transduced (sgRNA 1). Subsequently, control or *CFLAR* sgRNA was transduced, and whole cell lysates were prepared 5 days thereafter. (E) Immunoblot analysis of stable HA-cFLIP-S or V5-GFP expressing GM12878, 5 days after transduction with control or *CFLAR* sgRNA. * marks a non-specific band. Arrow indicates endogenous cFLIP-S band. (F) Fold-change of live GM12878 cell numbers, 5 days after *CFLAR* versus control sgRNA transduction. Small molecules inhibitor or DMSO vehicle control were added 1 days after sgRNA transduction and refreshed 48 hours later, as indicated. **p<0.01, ****p<0.0001.

Figure S5

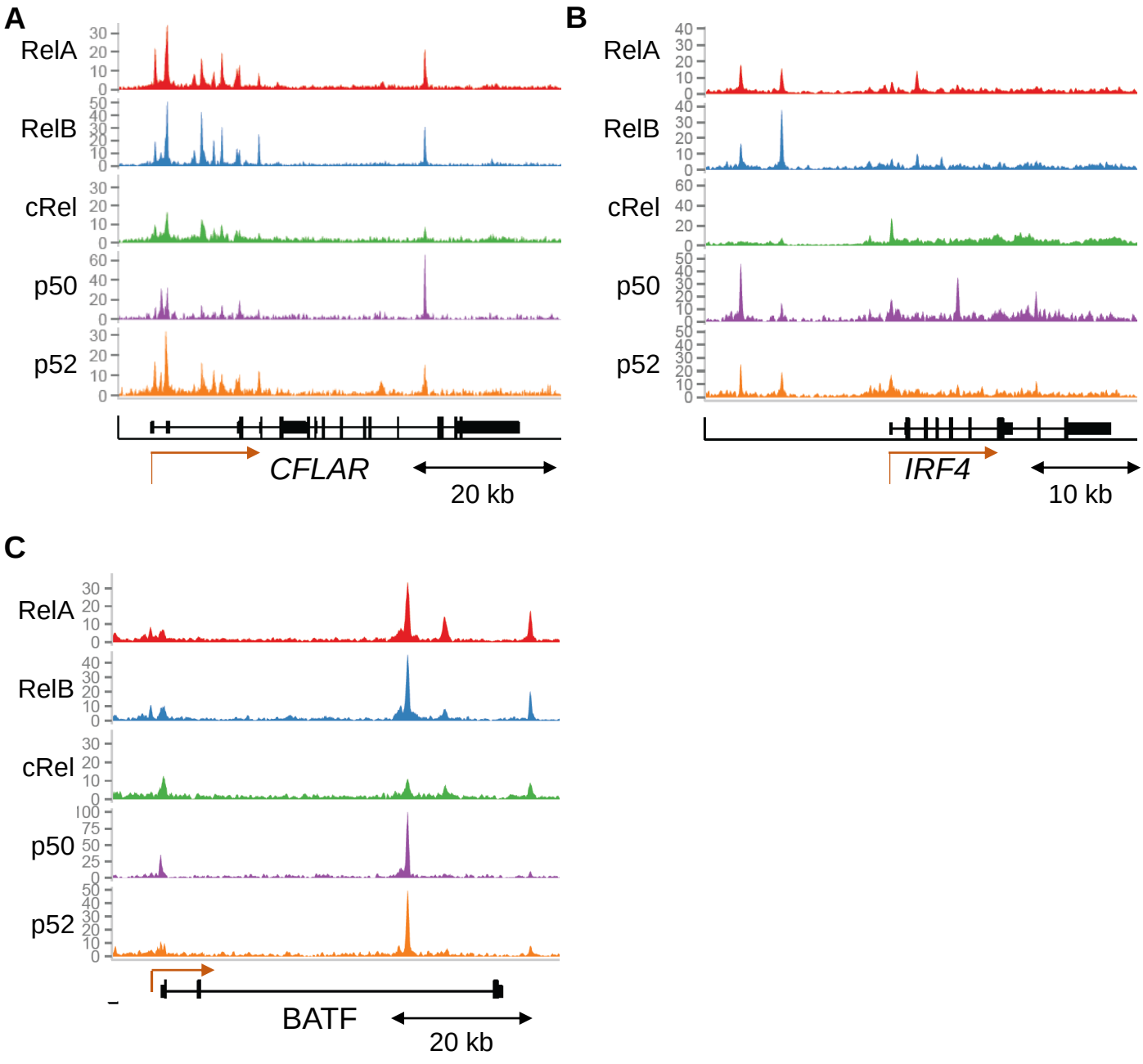

Figure S5 LMP1-Activated NF-kB subunits at CFLAR, IRF4 and BATF loci, related to Figure 4-5. GM12878 ChIP-seq (Zhao et al, 2014) signals for the NF-κB subunits RelA, RelB, cRel, p50 and p52 at the (A) *CFLAR*, (B) IRF4 and (C) BATF loci.

Figure S6

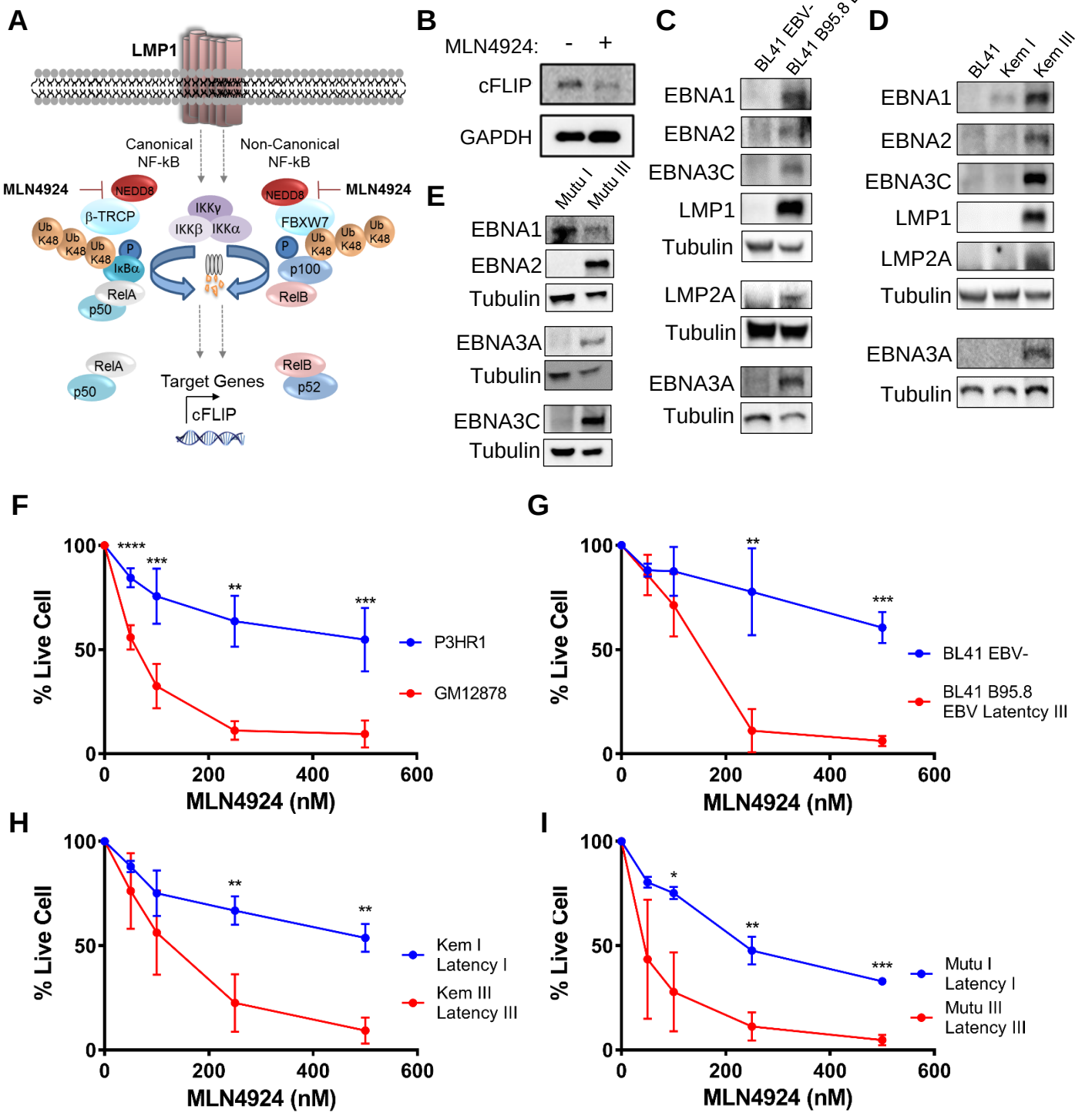

Figure S6. The EBV Latency III Growth Program Sensitizes B-cells to the Neddylation Inhibitor MLN4924, Related to Figure 4. (A) Schematic model of MLN4924 inhibition of the cullin ubiquitin ligases β-TRCP and FBXW7, which are essential for canonical and non-canonical NF-kB activation, respectively. (B) Immunoblot analysis of cFLIP expression in GM12878 treated with or without MLN4924 (1mM) for 24 hours. (C-E) Immunoblot analysis of whole cell lysates for EBV latency proteins, as indicated, in (C) EBV-negative BL41 vs. B95.8 EBV strain super-infected BL41 cells, (D) Kem BL cells with Latency I (Kem I) vs. Latency III (Kem III) expression patterns and (E) Mutu BL cells with Latency I (Mutu I) vs. Latency III (Mutu III) expression pattern. (F-I) Dose-response curves for the indicated cell line pairs treated with MLN4924 for 48 hours. (F) GM12878 vs. P3HR1 cells; (G) BL41 vs. BL41 B95.8; (H) Kem I vs. Kem III; (I) Mutu1 vs. MutuIII. Average and standard deviation values from triplicate experiments are shown. *, p <0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.

Figure S7

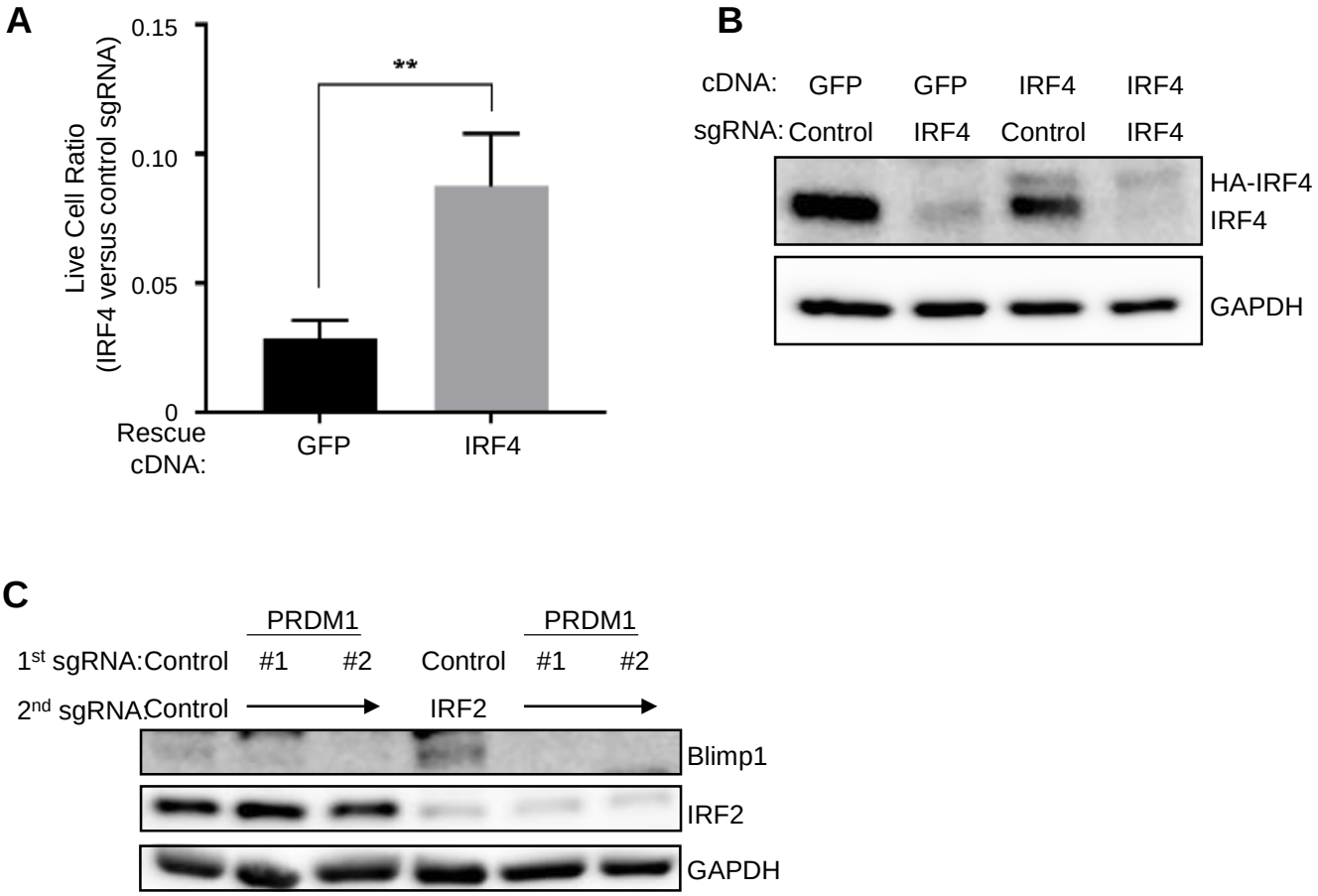

Figure S7 LCLs are Addicted to EBV Oncoprotein Targeted IRF2 and IRF4, related to Figures 5-7. (A) cDNA rescue of *IRF4*-sgRNA-transduced LCLs. GM12878 stably expressing the indicated rescue cDNAs were transduced with lentiviruses expressing control or *IRF4* sgRNA. 1 week after transduction, live cell ratios of *IRF4*- to control-sgRNA-transduced cells were quantitated. Values from biological triplicate experiments are shown. **, $p<0.01$. (B) GM12878 stably expressing GFP or IRF4 rescue cDNA were transduced with lentivirus expressing GFP or *IRF4* sgRNA. 5 days later, cDNA expression in whole cell lysates was evaluated by immunoblot. (C) Immunoblot analysis of whole cell lysates from GM12878 with control versus *PRDM1* sgRNAs expression (1st sgRNA), followed by expression of control or *IRF2* sgRNAs (2nd sgRNA), as indicated. Immunoblots are representative of three independent experiments.