Supplemental Data

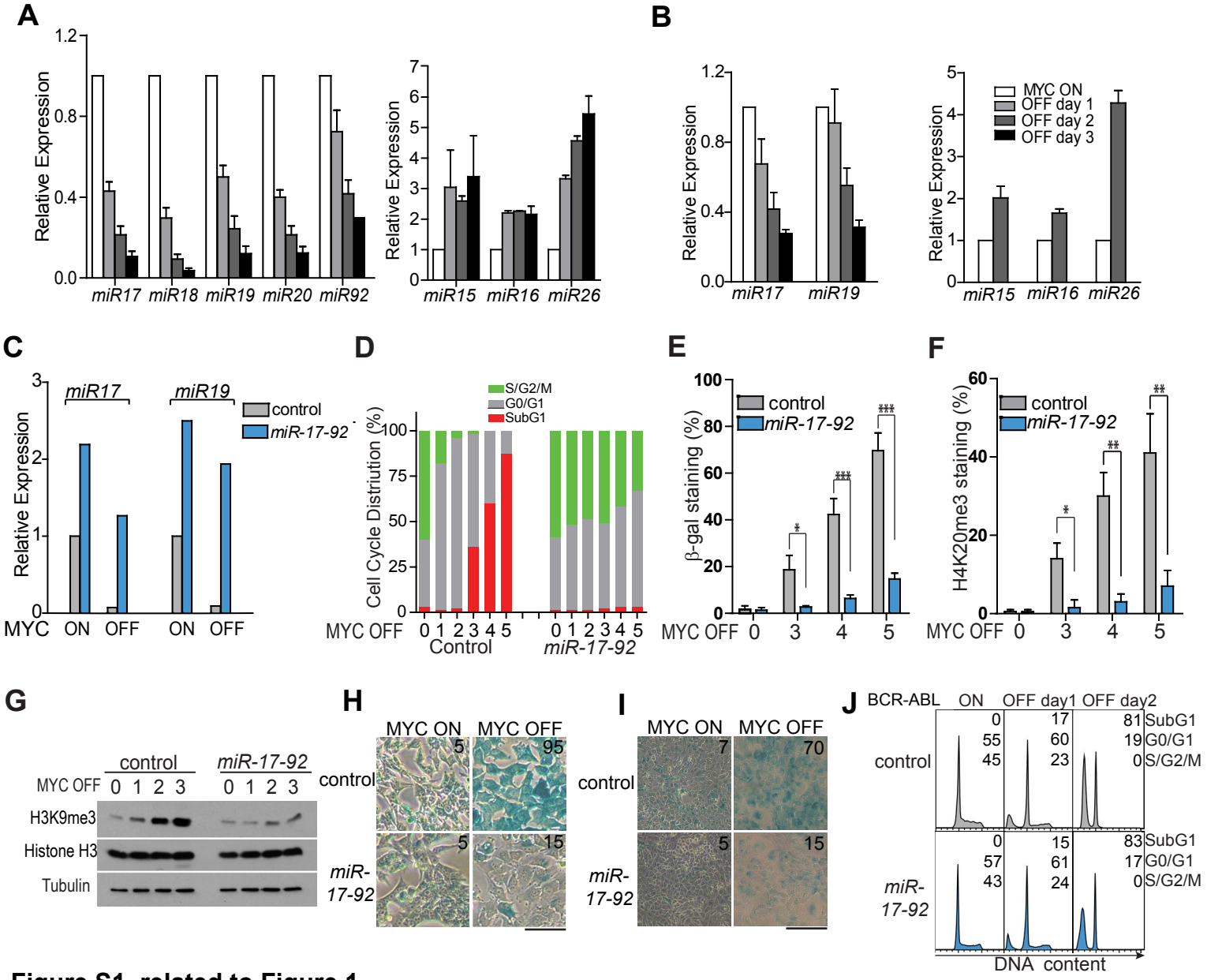

Figure S1, related to Figure 1.

(A & B) Changes of *miR-17-92*, *miR-15/16*, and *miR-26* upon MYC inactivation in (A) three *Eμ-tTA/tet-O-MYC* lymphomas and (B) *LAP-tTA/tet-O-MYC* hepatocellular carcinoma. The microRNA real-time PCR data were normalized to *U6* snRNA. Data are presented as mean+/-SEM.

(C) Quantification of *miR-17* and *miR-19* in *Eμ-tTA/tet-O-MYC* lymphoma with retroviral *miR-17-92* expression. The MYC OFF samples were collected at three days of MYC inactivation

(D) Cell cycle distribution of lymphoma cells. The flow cytometric plots are shown in Figure 1C.

(E & F) Quantification of the SA-β-gal staining and H4K20me3 staining following MYC inactivation. Data are presented as mean+/-SEM. Student's t test. *p<0.05, **p<0.01, ***p<0.001.

(G) Induction of H3K9me3 upon MYC inactivation as shown by western blot analysis. Histone H3 and tubulin served as loading controls.

(H & I) SA-β-gal staining of hepatocellular carcinoma line EC4 (H) and osteosarcoma line 1325 (I) three days after MYC inactivation. Numbers in upper right quadrant indicate percentage of cells stained positive. Scale bar = 50μm.

(J) Cell cycle distribution upon BCR-ABL inactivation in B-cell leukemia. The BCR-ABL-driven murine B-cell acute lymphoblastic leukemia cell lines were derived from the *Eμ-tTA/tet-O-BCR-ABL* mice.

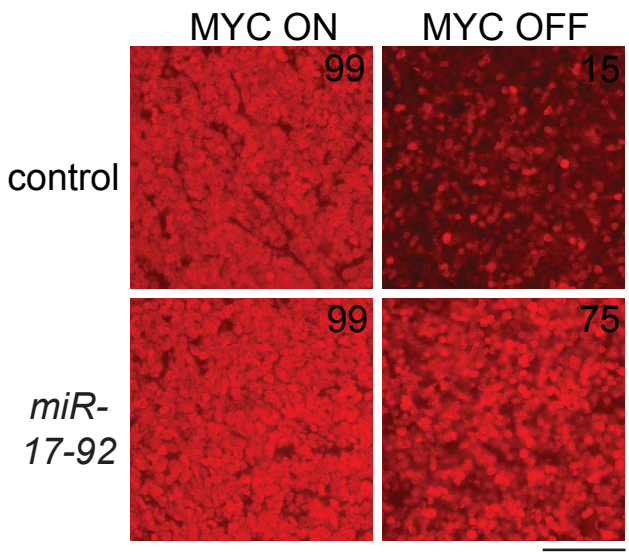

Figure S2, related to Figure 2. Ki67 staining of tumors upon MYC inactivation.

FVB/N host mice with control or *miR-17-92*-expressing tumors were treated with doxycycline for four days before tumor collection. The ki67 positive cells were stained red. Numbers in upper right quadrant indicate percentage of cells stained positive. Scale bar = 50μm.

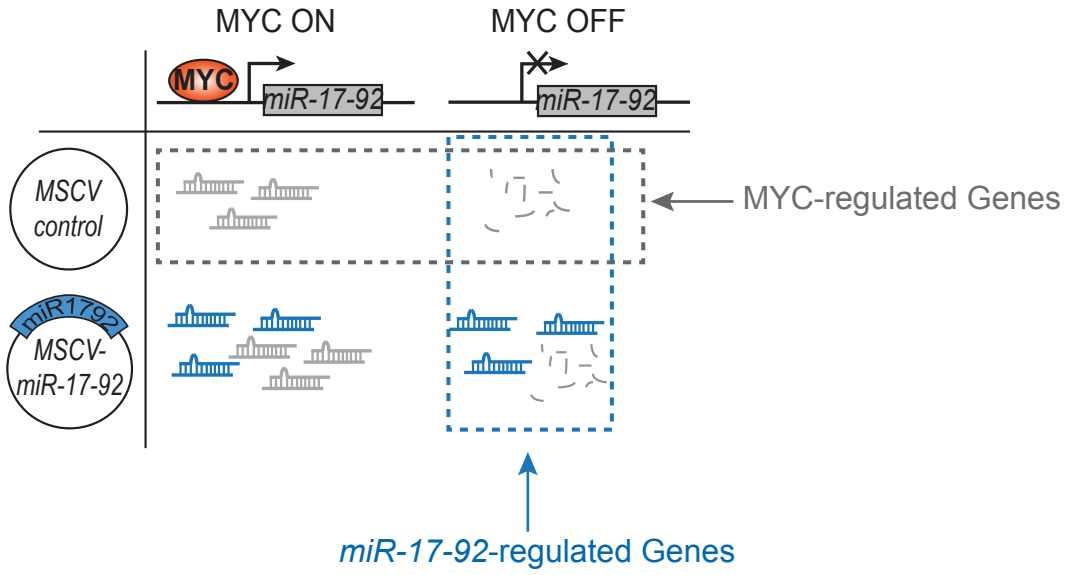

Figure S3, related to Figure 3. Comparison of microarray gene expression profiles to define the MYC-regulated versus *miR-17-92*-regulated genes.

Genes that were differentially expressed between MYC ON and MYC OFF conditions in the control lymphoma cells were defined as the MYC-regulated genes (grey dashed line). Genes that were differentially expressed between control and *miR-17-92* lymphoma cells under the MYC OFF condition were defined as the *miR-17-92*-regulated genes (blue dashed line). The overlap between MYC-regulated genes and *miR-17-92*-regulated genes is further shown in Figure 3A.

Table S1, related to Figure 3. Provided as separate Excel files.

A list of genes upregulated by both MYC and *miR-17-92*.

Table S2, related to Figure 3. Provided as separate Excel files.

A list of genes downregulated by both MYC and *miR-17-92*.

Table S3, related to Figure 3. Provided as separate Excel files.

Genes with multiple *miR-17-92* binding sites.

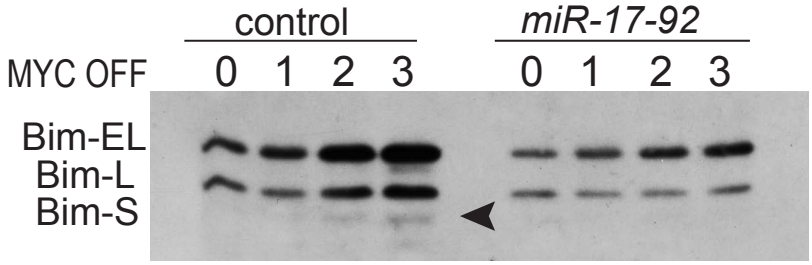

Figure S4, related to Figure 4.

A blot with a longer time exposure of the same Bim western blot shown in Figure 4A. The three isoforms of Bim protein are labeled on the left side of the blot with Bim-S indicated by an arrowhead.

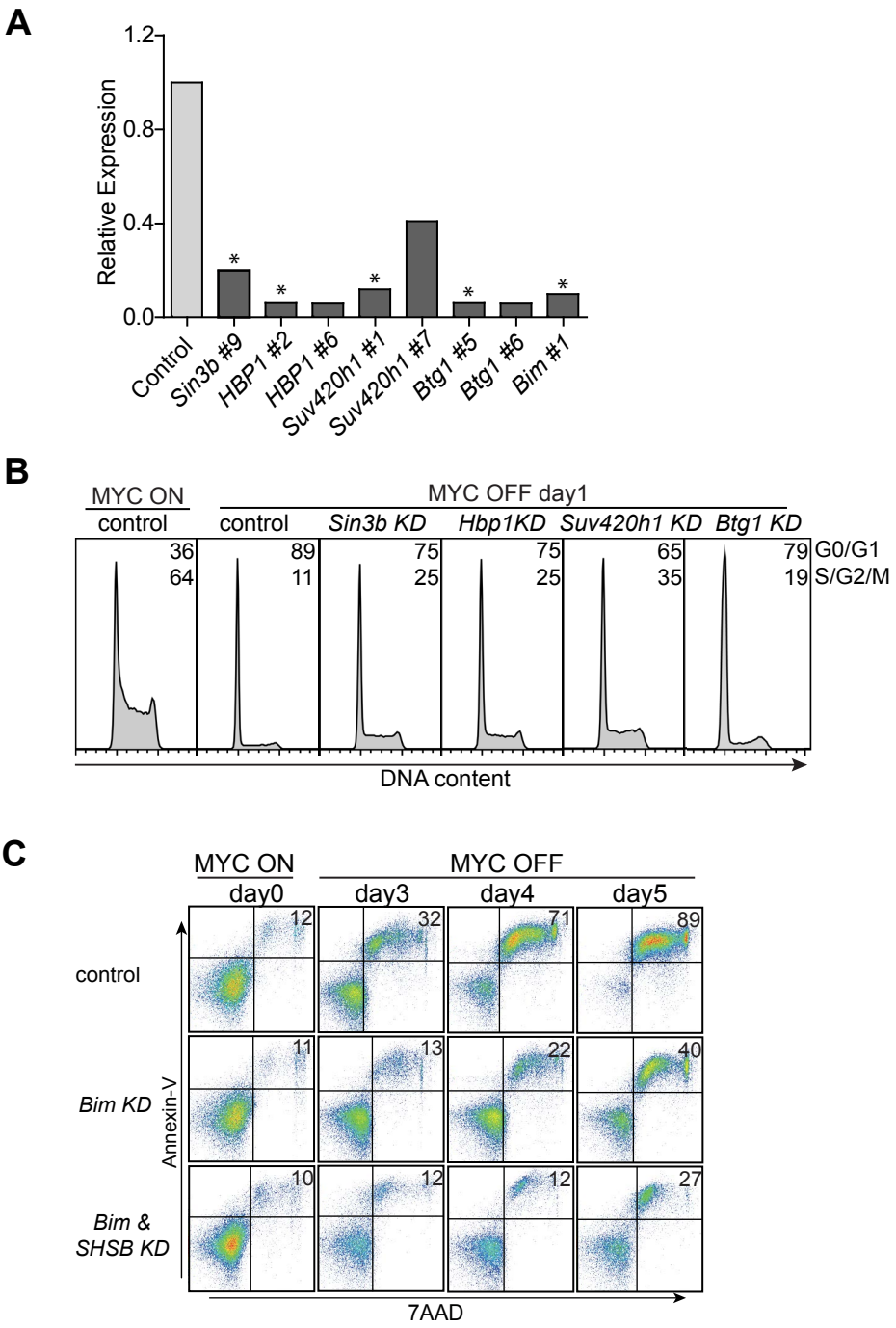

Figure S5, related to Figure 5.

(A) Knockdown efficiency of shRNAs. Samples were collected after MYC inactivation for 2 days. Expression levels of individual knockdowns were quantified by real-time PCR and normalized to level of *Ubiquitin C*. Expression level in cells with scrambled control shRNA was set to 1. The shRNAs used in the combinatorial knockdown are indicated by asterisks.

(B) Cell cycle distribution of cells with individual knockdowns of chromatin modifiers *SHSB* and *Bim*. MYC OFF samples were taken at 24 hours of MYC inactivation. Numbers indicate percentage of cells in either G1/G0 or G2/S/M phase of cell cycle.

(C) Apoptosis of tumor cells with *Bim* and *SHSB* knockdown upon MYC inactivation. The control cells, cells with *Bim* knockdown, and cells with *Bim&SHSB* knockdown were stained with 7-AAD/Annexin V and analyzed by flow cytometry. Numbers in the top right quadrants indicate percentage of cells undergoing apoptosis.

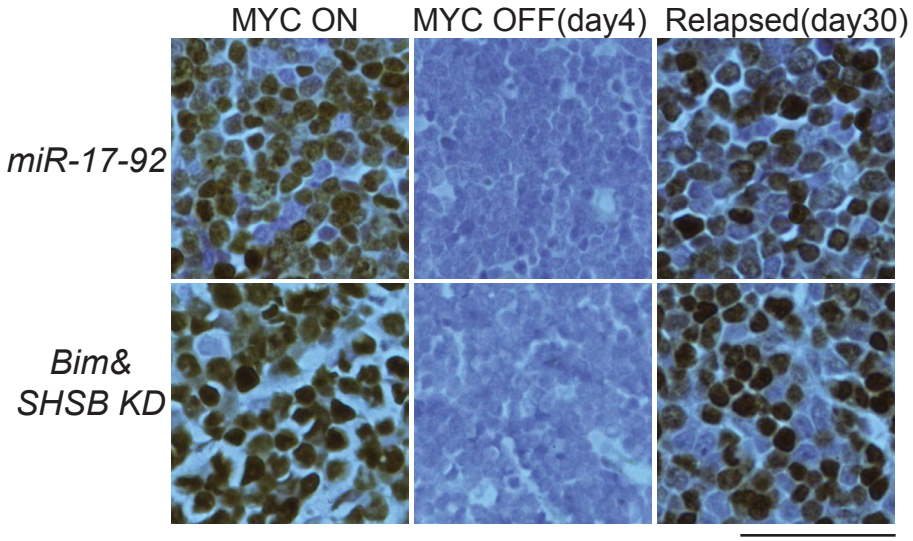

Figure S6, related to Figure 6. Immunohistochemical staining of MYC in the regressing and relapsed tumors.

Prior to MYC suppression, MYC protein expression was high, whereas after MYC suppression, MYC protein expression was not detectable in the regressing tumors. After prolonged MYC suppression, the relapsed tumors expressed high levels of MYC protein. Tumor slides were stained with DAB (dark brown) and counterstained with hematoxylin (blue). The antibody (Epitomics) recognizes both mouse and human MYC. Scale bar = 50μm.