



**Figure S6. *Setd2* deficiency triggers replication stress.**

(A) Two-dimensional diagram analysis of differentially expressed genes between KO and WT BM LSKs of mice at 4 weeks after pl-pC induction. Fold change  $\geq 2$  and  $P < 0.05$  as a screening parameter. (B-C) GO biological analysis of down- (B) and up-regulated (C) genes in KO BM LSK cells relative to WT group. (D) q-PCR detection of deregulated genes. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . (E) Basic statistics for quality

control of WGBS sequencing data. (F) Comprehensive analysis of deregulated genes with DNA methylation change. The mRNA level of *LTBP3* with DNA hyper-methylation at CGI region was downregulated in KO LSKs (up), and that of *Gata3* with DNA hypo-methylation at CGI region was upregulated in KO LSKs (down). (G) The Comparison of global DNA methylation level at different genome regions between WT and KO LSKs from mice at 4 weeks after pl-pC injection. (H) Distribution analysis of CpG and non-CpG DNA methylation at *Klf1* genome locus in WT and KO LSKs from mice at 4 weeks after pl-pC injection. (I) FACS analysis of c-Kit expression in KO Lin<sup>-</sup> BM cells transfected with *Klf1*-shRNA. (J) Representative cell cycle analysis of BM FLT3<sup>-</sup>(top) and FLT3<sup>+</sup>-LSKs (bottom) from WT or KO mice at 4 weeks after pl-pC induction by using Ki67 staining. (K) Cell apoptosis analysis of BM FLT3<sup>-</sup>- and FLT3<sup>+</sup>-LSKs from WT or KO mice at 4 weeks after pl-pC induction by using Annexin V staining. n=4. (L) Representative FACS analysis of HSPC subsets in KO BM relative to that in WT BM at day 20 after single time 5-FU treatment. (M) Representative FACS analysis of BM FLT3<sup>-</sup>(top) and FLT3<sup>+</sup>-LSKs (bottom) by *in vivo* BrdU administration at day 20 after single-time 5-FU treatment.