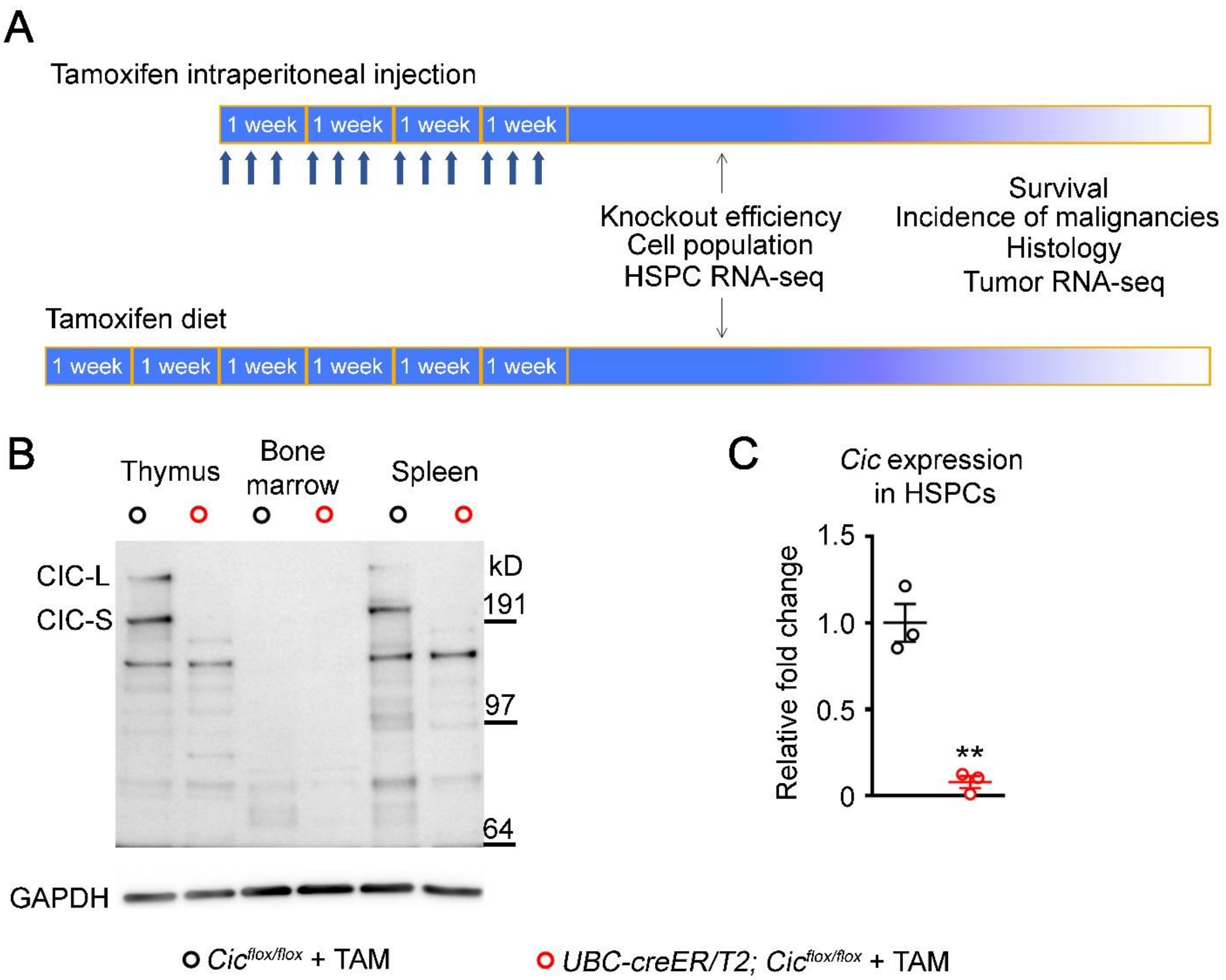

Fig. S1. Tamoxifen treatments and Cre-mediated knockout efficiency of *Cic*. (*A*) Two regimens of tamoxifen treatments. *Cic*$^{flox/flox}$ and *UBC-cre/ERT2; Cic*$^{flox/flox}$ mice at 8-12 weeks of age were given tamoxifen via intraperitoneal injection for four weeks, or mice at 6-10 weeks of age were fed a tamoxifen diet for six weeks. (*B*) Western blot showing CIC-L and CIC-S isoforms were deleted from the thymus and spleens of *UBC-cre/ERT2; Cic*$^{flox/flox}$ mice two weeks post tamoxifen (TAM) treatment. (*C*) Quantitative PCR of *Cic* expression in hematopoietic stem and progenitor cells (HSPCs, defined as Lineage$^-$ Sca-1$^+$ c-Kit$^+$) (n = 3 animals). Data are presented in scatter plots with error bars representing mean ± SEM. Statistical analysis was performed using a two-tailed unpaired t test. **, $P < 0.01$.

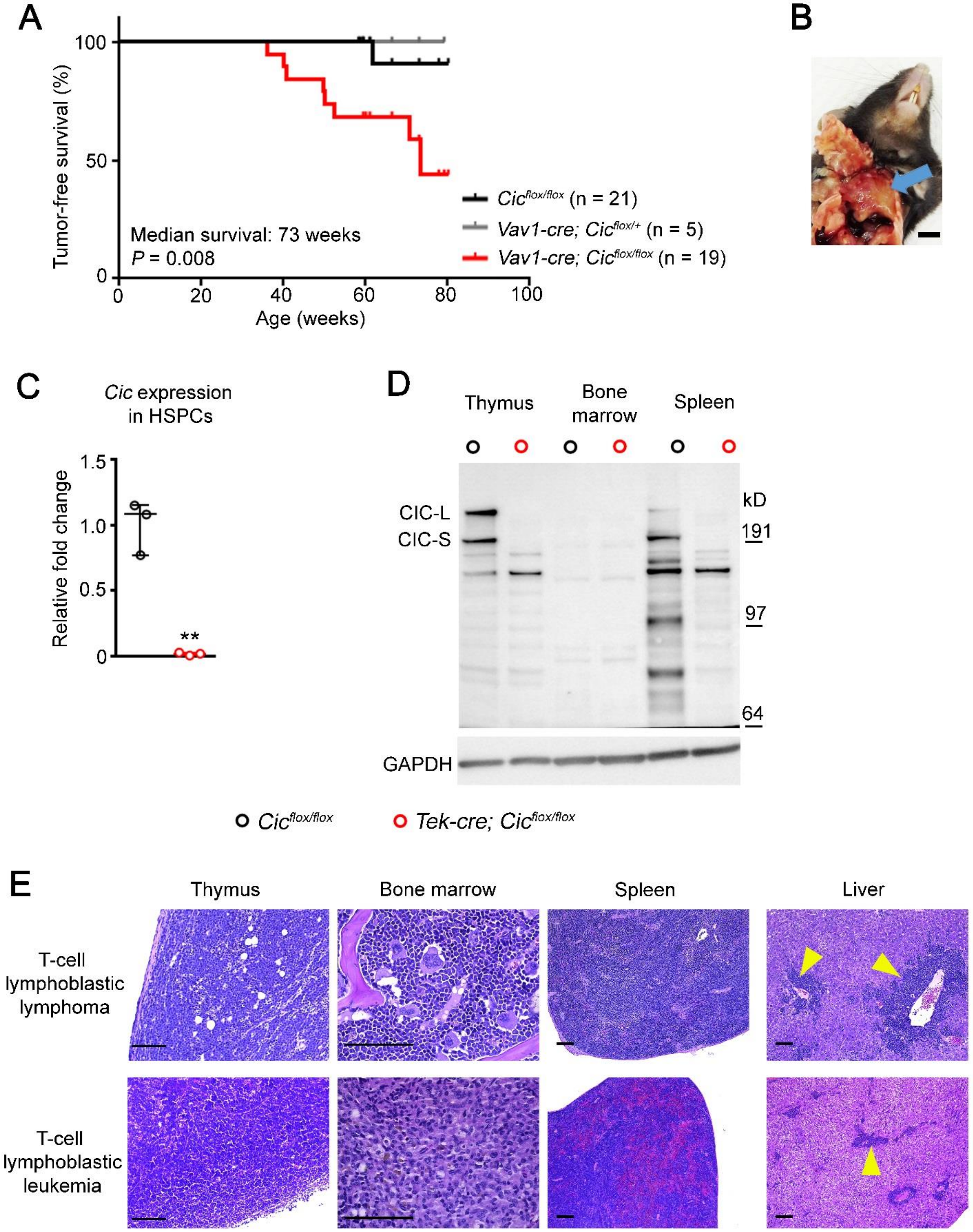
A
Tumor-free survival (%)
100
50
0
0
20
40
60
80
100
Age (weeks)
Median survival: 73 weeks
P = 0.008
Cicflox/flox (n = 21)
Vav1-cre; Cicflox/+ (n = 5)
Vav1-cre; Cicflox/flox (n = 19)
B
C
Cic expression in HSPCs
Relative fold change
1.5
1.0
0.5
0
**
D
Thymus
Bone marrow
Spleen
CIC-L
CIC-S
kD
191
97
64
GAPDH
Cicflox/flox
Tek-cre; Cicflox/flox
E
Thymus
Bone marrow
Spleen
Liver
T-cell lymphoblastic lymphoma
T-cell lymphoblastic leukemia

Fig. S2. Loss of *Cic* in hematopoietic cells causes T-cell lymphoblastic leukemia/lymphoma (T-ALL). (*A*) Tumor-free survival of *Vav1-cre; Cic*$^{flox/flox}$ mice. (*B*) Representative image of a lymphoma found in the *Vav1-cre; Cic*$^{flox/flox}$ mice. Arrow points to the tumor. Scale bar = 0.5 cm. (*C*) Quantitative PCR of *Cic* expression in hematopoietic stem and progenitor cells (HSPCs) from *Cic*$^{flox/flox}$ and *Tek-cre; Cic*$^{flox/flox}$ mice (n = 3 animals). Data are presented in scatter plots with error bars representing mean ± SEM. Statistical analysis was performed using two-tailed unpaired t test. **, $P < 0.01$. (*D*) Western blot showing CIC-L and CIC-S isoforms were deleted from the thymus and spleens of *Tek-cre; Cic*$^{flox/flox}$ mice. (*E*) Histology of a *Tek-cre; Cic*$^{flox/flox}$ mouse with T-cell lymphoblastic lymphoma (upper panels) and one with T-cell lymphoblastic leukemia (lower panels). Arrowheads point to malignant lymphocytes in the liver. Scale bars = 100 μm.

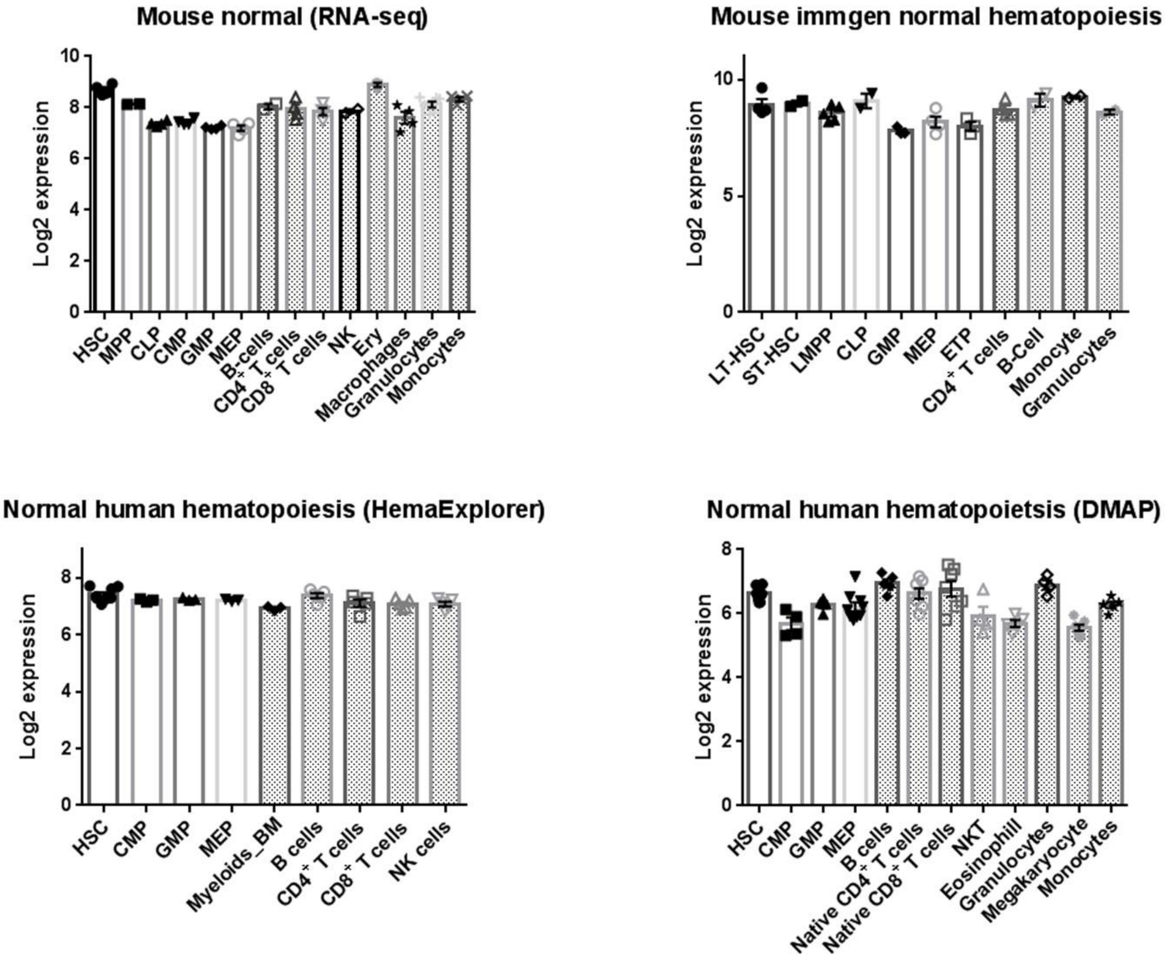

Fig. S3. *CIC* gene expression during normal hematopoiesis in mice and humans. Expression data were extracted from the BloodSpot database.

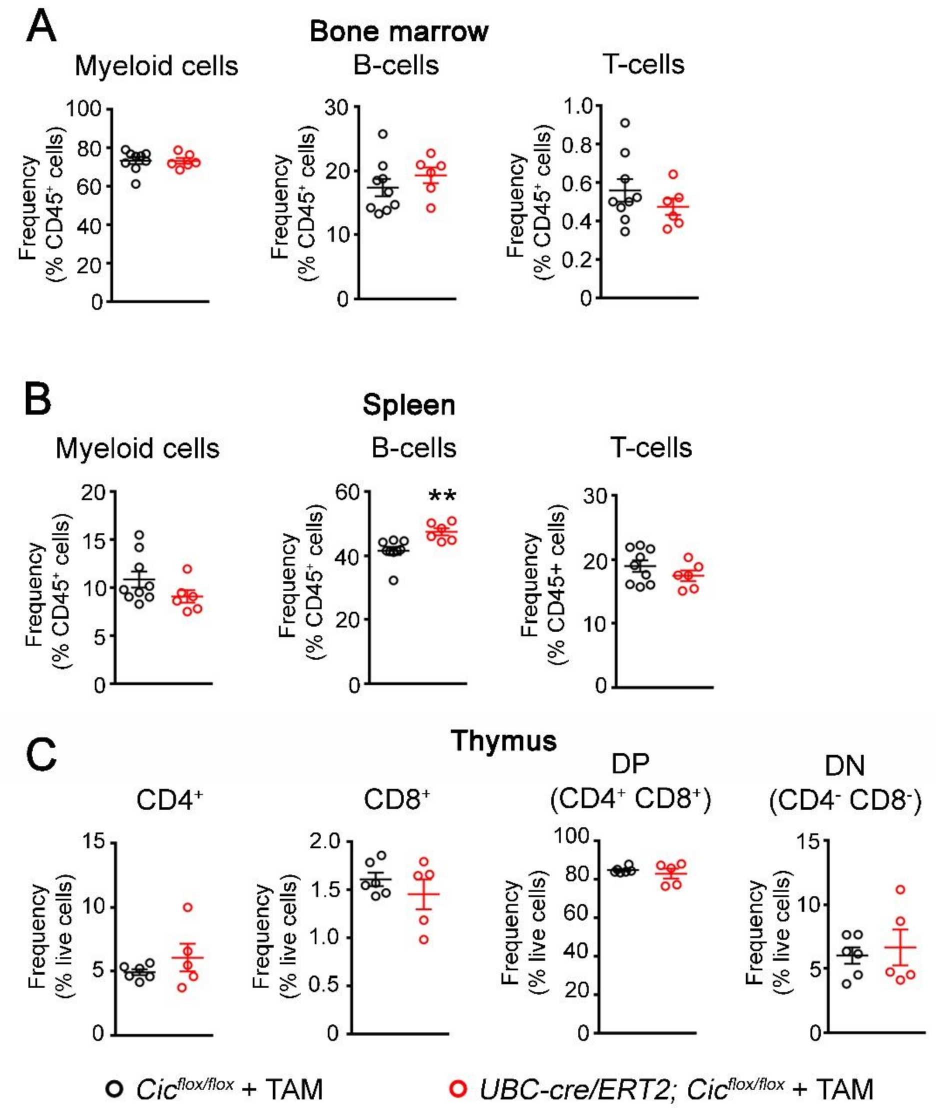

Fig. S4. Flow cytometry analyses of hematopoietic cells in the *UBC-cre/ERT2; Cic$^{flox/flox}$* mice two weeks post tamoxifen treatment. (*A*) Lineage analyses of the bone marrow. (*B*) Lineage analyses of the spleen. (*C*) T-cell analyses of the thymus. Myeloid cells, Mac-1$^+$ (CD11b$^+$) or Gr-1$^+$; B cells, B220$^+$; T cells, CD4$^+$ or CD8$^+$; DP, double positive (CD4$^+$ CD8$^+$); DN, double negative (CD4$^-$ CD8$^-$). Data are presented in scatter plots with error bars representing mean ± SEM (n = 5-6 animals). Statistical analysis was performed using two-tailed unpaired t test. **, *P* < 0.01.

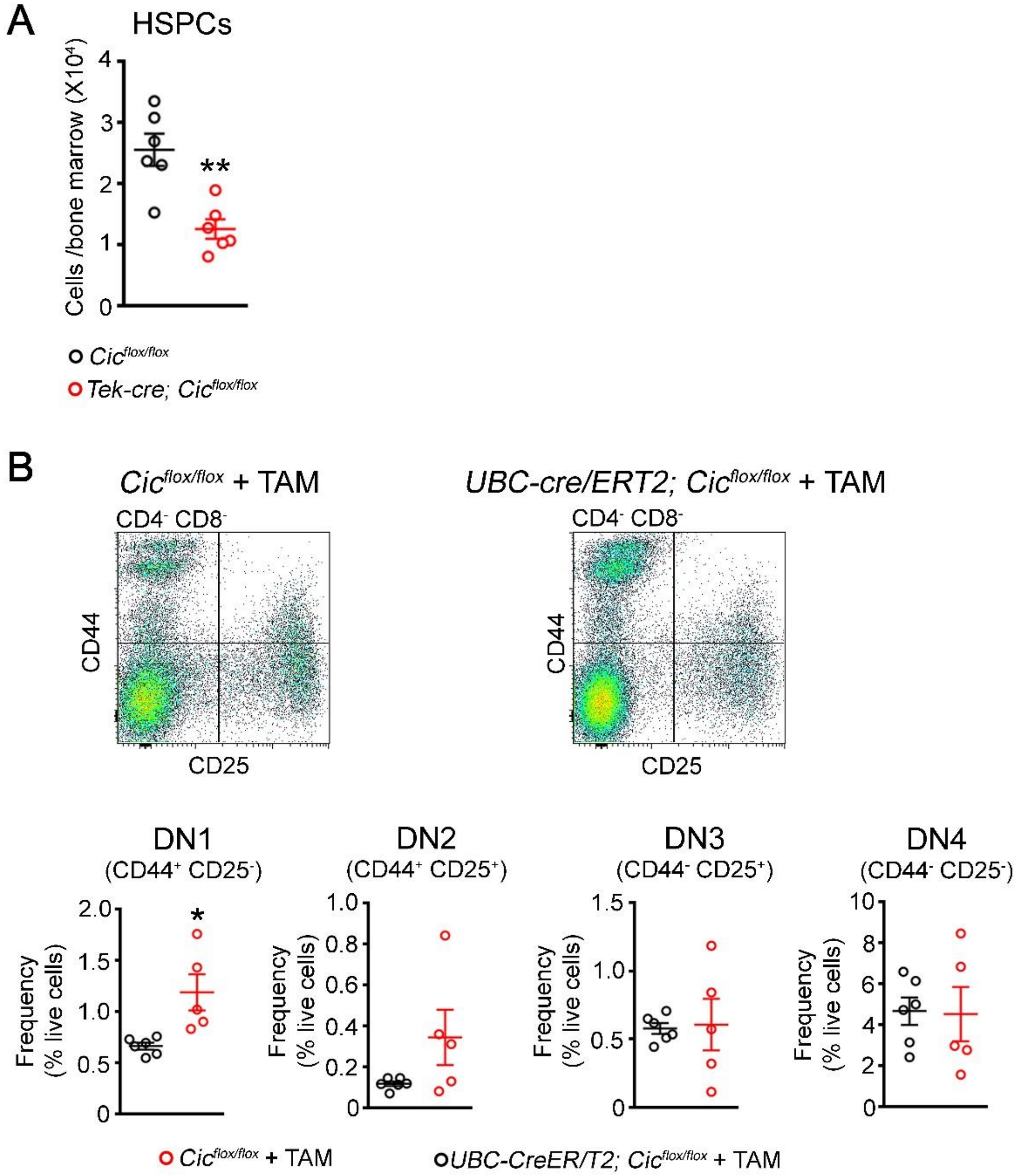

Fig. S5. Loss of CIC disrupts the homeostasis of progenitor cells. (*A*) Analysis of hematopoietic stem and progenitor cells (HSPCs, Lineage$^-$ c-Kit$^+$ Sca-1$^+$) in 12-week old *Cic*$^{flox/flox}$ and *Tek-cre; Cic*$^{flox/flox}$ mice (n = 6 animals). (*C*) Analysis of CD4$^-$ CD8$^-$ double negative (DN) compartments in the thymus from *Cic*$^{flox/flox}$ and *UBC-cre/ERT2; Cic*$^{flox/flox}$ mice two weeks post tamoxifen treatment (n = 5-6 animals). Representative flow cytometry data are shown at the top panel. Please note that these analyses were performed using a separate cohort of animals from those presented in **Fig. 3**. The increase in DN1 frequency in the *Cic* adult knockout mice was observed in both cohorts. Data are presented in scatter plots with error bars representing mean ± SEM. Statistical analyses were performed using two-tailed unpaired t test. *: $P < 0.05$; **: $P < 0.01$.

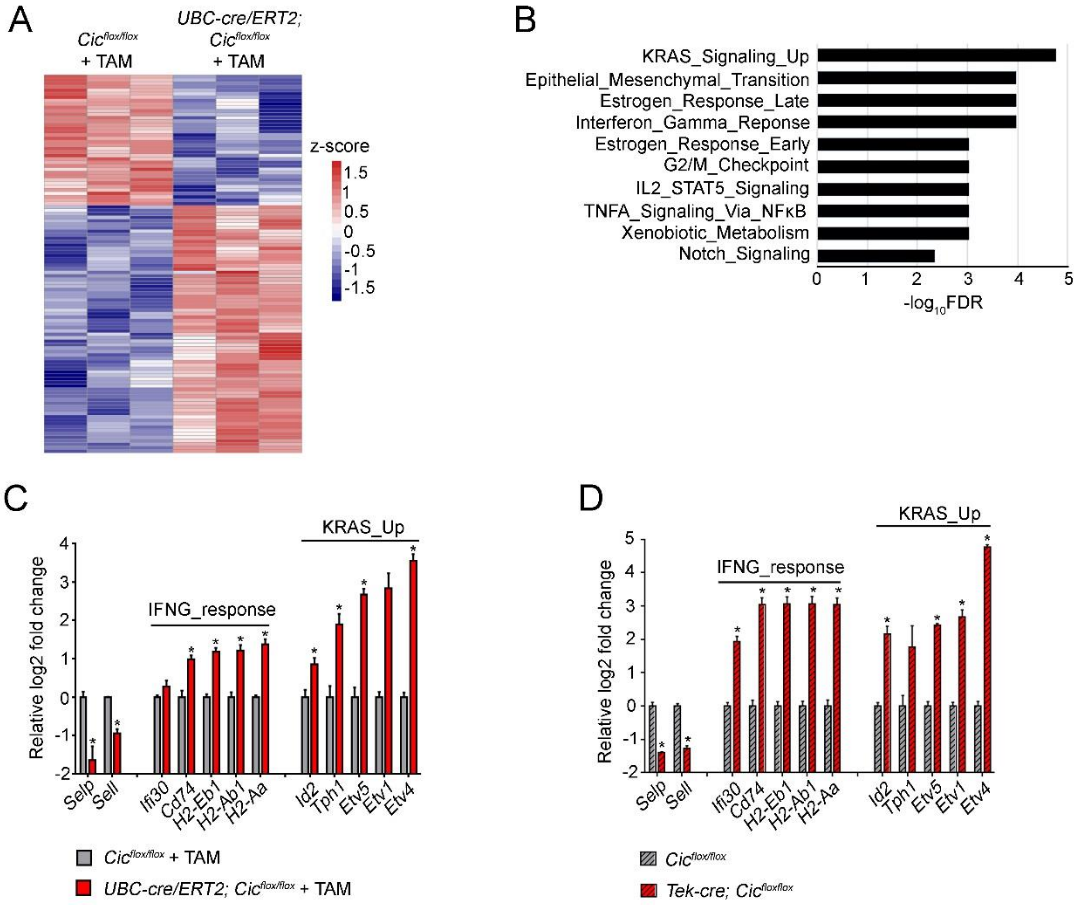

Fig. S6. Gene expression profiling of hematopoietic stem and progenitor cells (HSPCs) from *Cic* adult knockout mice and controls. (*A*) Heatmap showing clustering of differentially expressed genes (DEGs, FDR < 0.05) from the RNA-seq study. HSPCs were isolated two weeks post tamoxifen treatment (n = 3). (*B*) Top 10 hallmark gene sets that showed significant overlap with the up-regulated genes in HSPCs from *Cic* adult knockout mice. (*C*) Quantitative PCR validating DEGs from the RNA-seq study (n = 3 animals). KRAS_Up, genes upregulated by KRAS activation. IFNG response, genes up-regulated in response to interferon gamma. (*D*) Quantitative PCR showing similar gene expression changes in the HSPCs from 12-week old *Tek-cre; Cic*$^{flox/flox}$ mice (n = 3 animals). Error bars represent mean + SEM. Statistical analyses were performed using multiple t tests with a false discovery rate (FDR) approach. *: FDR < 0.05.

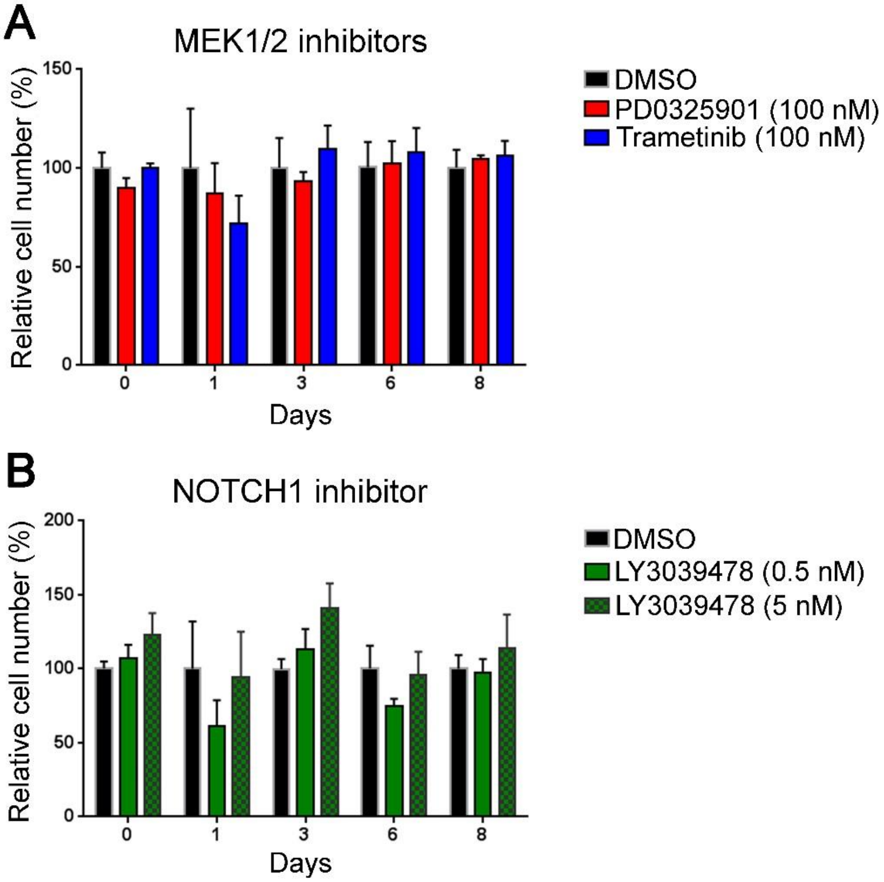

Fig. S7. *Cic*-null tumors are insensitive to MAPK and NOTCH1 inhibition. Treatment of cultured *Cic*-null tumor cells with inhibitors for MEK1/2 (*A*), or a NOTCH1 inhibitor (*B*). Error bars represent mean ± SEM. Four technical repeats for each treatment. Statistical analyses were performed using regular two-way ANOVA with Turkey’s correction for multiple comparisons.

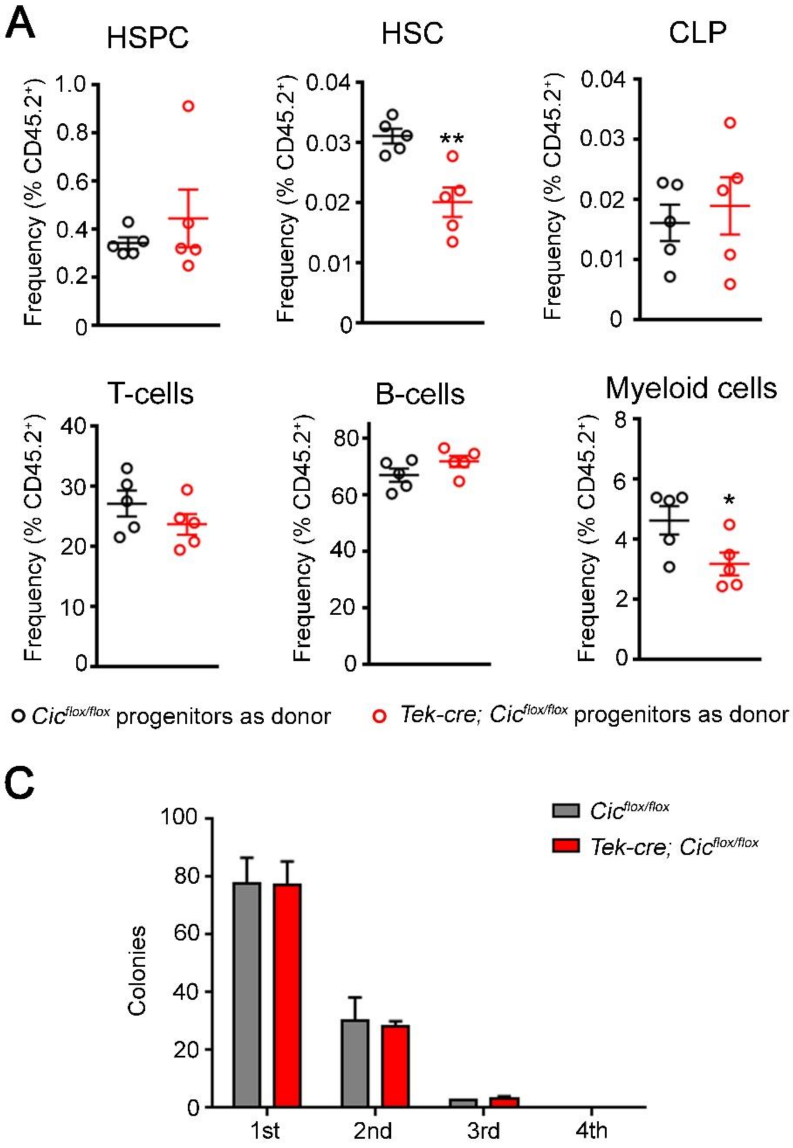

Fig. S8. *Cic*-knockout progenitors show slightly reduced ability to generate mature myeloid cells *in vivo*. (*A*) *Cic*$^{flox/flox}$ or *Tek-cre; Cic*$^{flox/flox}$ progenitors (both CD45.2) were transplanted into wildtype CD45.1 recipients. The frequencies of hematopoietic stem and progenitor cells (HSPC), hematopoietic stem cells (HSC), common lymphoid progenitors (CLP) in the bone marrow, as well as T-cells, B-cells and Myeloid cells in the peripheral blood were analyzed eight weeks after transplantation. (*B*) Colony-forming unit assay plating 1000 *Cic*$^{flox/flox}$ or *Tek-cre; Cic*$^{flox/flox}$ c-Kit$^+$ cells. Every seven days colonies were counted and 1000 cells were re-plated up to four rounds of plating. Results were plotted as mean ± SEM. Statistical analyses were performed using two-tailed unpaired t tests. *: $P < 0.05$; **: $P < 0.01$.

Tumor ID	**Tumor-free survival age (weeks post tamoxifen treatment)**	**Tumor immunophenotype**	**T-cell lymphoblastic lymphoma or leukemia**
KO-1	56	75% $CD4^+$; 25% $CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
KO-2	33	70% $CD4^+$; 30% $CD4^+$ $CD8^+$	T-cell lymphoblastic leukemia; 71% $CD4^+$; 28% $CD4^+$ $CD8^+$ T-cells in the bone marrow
KO-3	27	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
KO-4	20	$CD4^+$	T-cell lymphoblastic lymphoma
KO-5	21	$CD4^+$	T-cell lymphoblastic leukemia; 65% $CD4^+$ T-cells in the bone marrow
KO-6	21	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
KO-7	26	40% $CD4^+$ $CD8^+$; 60% $CD8^+$	T-cell lymphoblastic lymphoma
KO-8	39	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma

Supplemental Table S1. Summary of eight tumors from the *UBC-cre/ERT2; Cic*$^{flox/flox}$ mice treated with tamoxifen.

Tumor ID	Tumor-free survival age	Tumor immunophenotype	T-cell lymphoblastic lymphoma or leukemia
TKO 1	62	$CD4^+$	T-cell lymphoblastic leukemia
TKO 2	37	$CD4^+$	T-cell lymphoblastic lymphoma
TKO 3	60	50% $CD4^+$, 50% $CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
TKO 4	45	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
TKO 5	44	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
TKO 6	69	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
TKO 7	40	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
TKO 8	56	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma

Supplemental Table S2. Summary of eight tumors from the Tek-*cre; Cic*$^{flox/flox}$ mice.

Tumor ID	**Tumor-free survival age (weeks post tamoxifen treatment)**	**Tumor immunophenotype**	**T-cell lymphoblastic lymphoma or leukemia**
BMTP-1	43	$CD4^+$	T-cell lymphoblastic lymphoma
BMTP-2	30	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
BMTP-3	26	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
BMTP-4	25	$CD4^+$ $CD8^+$	T-cell lymphoblastic lymphoma
BMTP-5	27	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
BMTP-6	30	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
BMTP-7	30	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
BMTP-8	19	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma
BMTP-9	27	Not determined. Histological findings confirmed T-cell lymphoblastic lymphoma.	T-cell lymphoblastic lymphoma

Supplemental Table S3. Summary of nine tumors from the wildtype mice transplanted with progenitor cells from *UBC-cre/ERT2; Cic*$^{flox/flox}$ mice and treated with tamoxifen.

		Notch1 (uc008ivl.2)				**Kras (uc009erh.2)**			**Nras (uc008qsm.1)**			**Pten (uc008hfr.1)**			
Genotype/description	**Tumor immonophenotype**	Exon 26	Exon 27	Exon 28	Exon 34	Exon 2	Exon 3	Exon 4	Exon 2	Exon 3	Exon 4	Exon 5	Exon 6	Exon 7	Exon 8
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	50% CD4+; 15% CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	70% CD4+; 30% CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	CD4+ CD8+	-	-	-	S2407fs	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+ CD8+	-	-	-	R2361fs	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	Q171L	-	-

		Idh1 (uc007bhn.2)	**Flt3 (uc009aob.2)**			**Ptpn11 (uc008zio.2)**		**Fbxw7 (uc008pqk.2)**					
Genotype/description	**Tumor immonophenotype**	Exon 3	Exon 13	Exon 14	Exon 20	Exon 3	Exon 13	Exon 9	Exon 10	Exon 11	Exon 12	Exon 13	Exon 14
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	50% CD4+; 15% CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	70% CD4+; 30% CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ + TAM	CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-
UBC-cre/ERT2; Cic$^{flox/flox}$ as donor cells in bone marrow transplantation + TAM	CD4+ CD8+	-	-	-	-	-	-	-	-	-	-	-	-

Table S4. Sanger sequencing results for *Cic*-null tumors.

NAME	SIZE	NES	FDR q-val	RANK AT MAX	LEADING EDGE
HALLMARK_MYC_TARGETS_V2	58	3.1735077	0	3964	tags=76%, list=14%, signal=89%
HALLMARK_MYC_TARGETS_V1	197	3.092106	0	7434	tags=69%, list=27%, signal=94%
HALLMARK_E2F_TARGETS	193	2.7405202	0	8175	tags=61%, list=30%, signal=87%
HALLMARK_MTORC1_SIGNALING	193	2.252036	0	6426	tags=47%, list=24%, signal=61%
HALLMARK_UNFOLDED_PROTEIN_RESPONSE	111	2.198831	0	8969	tags=64%, list=33%, signal=95%
HALLMARK_OXIDATIVE_PHOSPHORYLATION	192	2.0776792	0	9980	tags=66%, list=37%, signal=103%
HALLMARK_G2M_CHECKPOINT	190	1.9681258	0.00177362	8087	tags=52%, list=30%, signal=73%
HALLMARK_DNA_REPAIR	135	1.6385499	0.01130314	9187	tags=51%, list=34%, signal=77%
HALLMARK_NOTCH_SIGNALING	31	1.422112	0.03460204	3572	tags=35%, list=13%, signal=41%
HALLMARK_PANCREAS_BETA_CELLS	32	-2.0755568	0	3988	tags=53%, list=15%, signal=62%
HALLMARK_KRAS_SIGNALING_DN	173	-1.9046242	0	5207	tags=47%, list=19%, signal=58%
HALLMARK_APICAL_SURFACE	42	-1.6856445	0.00433567	5105	tags=43%, list=19%, signal=53%
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	190	-1.5927907	0.0122265	6273	tags=42%, list=23%, signal=54%
HALLMARK_MYOGENESIS	193	-1.523915	0.02601156	6362	tags=39%, list=23%, signal=50%
HALLMARK_APICAL_JUNCTION	187	-1.4613552	0.04909184	7068	tags=37%, list=26%, signal=50%
HALLMARK_ESTROGEN_RESPONSE_LATE	187	-1.4171898	0.07061846	5620	tags=32%, list=21%, signal=40%
HALLMARK_COAGULATION	121	-1.379649	0.09866883	6438	tags=36%, list=24%, signal=46%

Table S5. Gene set enrichment analysis (GSEA) for transcriptional profiles in *Cic*-null tumors.