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Supplementary Methods.

Patient information and immunohistochemistry (IHC)

87 patients diagnosed with de novo DLBCL at Nanfang Hospital, Guangzhou were included. All patients were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Clinical features of the patients were retrieved from the clinical database of Department of Hematology, Nanfang Hospital. The disease stage was evaluated according to the Ann Arbor staging system. Performance status was assigned according to the Eastern Cooperative Oncology Group (ECOG) scale. International prognostic index (IPI) score was calculated based on age, serum LDH, ECOG performance status, Ann Arbor stage and numbers of extra-nodal sites at diagnosis as previously described[1]. This study was approved by the Ethics Committee of Nanfang Hospital. Sections from formalin-fixed and paraffin-embedded diagnostic samples were collected for histological review and immunohistochemical analysis. IHC was carried out using a peroxidase-conjugated labeled dextran polymer method. Rabbit polyclonal to xCT was from Abcam (ab37185) with a dilution at 1:1000. 500 cells in 5 well-preserved areas were scored for the percentage of the positively stained cells. Positivity scores were assigned based on proportion of positively stained malignant cells: (1), 5-25%; (2), 26-50%; (3). 51-75%; (4), >75%. For COO sub-classification, CD10, BCL6, and Mum1 positivity was defined according to Hans et al[2].

Drug interaction study in xenograft mice

Ten million Riva or SuDHL2 cells (1 $X10^7$) were resuspended in HBSS and injected subcutaneously into the flank of 4- to 6-week-old NOD/SCID IL2Rγ-null (NSG) mice (The Jackson Laboratories). Treatment was initiated when tumors reach ~ 250 mg. Animals were randomly assigned to one of the 5 groups to be treated by vehicle, CHOP, SASP (150 mg/kg, i.p.), CHOP+SASP and pre-SASP+CHOP (pre-SASP, 150 mg/kg, i.p. was administered 3 days before CHOP). CHOP was administered once on day 0 as MTD for each component as previously published[3], that is cyclophosphamide “C”, 40 mg/kg, i.v., doxorubicin “H”, 1.6 mg/kg, i.v.; vincristine “O”, 0.5 mg/kg, i.v.; and prednisone “P”, 0.2 mg/kg, p.o. Tumor sizes were measured every 2-3 days using an electronic caliper. Tumor volume (mm3) was calculated using the formula of ($A \times B^2$)/2, where A and B are the tumor length and width in mm, respectively. Tumor growth inhibition (TGI) was calculated as TGI (%) = (Vc-Vt)/(Vc-Vo)*100, where Vc, Vt are the median tumor volume of control and treated groups at the end of the study and Vo is the median tumor volume at the start of the study. All mice were maintained and treated in compliance with IACUC approved protocols at Albert Einstein College of Medicine.

References Cited.

1. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1989;7(11):1630-1636.

2. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-282.

3. Mai Y, Yu JJ, Bartholdy B, et al. An oxidative stress-based mechanism of doxorubicin cytotoxicity suggests new therapeutic strategies in ABC-DLBCL. *Blood*. 2016;128(24):2797-2807.

sTable 1

Antibodies for Western Blot	Vendor	Catalog number	Dilution
xCT	Abcam	ab37185	1:1000
xCT (D2M7A)	Cell Signaling Technology	12691	1:1000
JNK (56G8)	Cell Signaling Technology	9258P	1:1000
p-JNK (T183/Y185) (81E11)	Cell Signaling Technology	4668P	1:1000
p38 (D13E1)	Cell Signaling Technology	8690P	1:1000
p-p38 (T180/Y182) (D3F9)	Cell Signaling Technology	4511P	1:1000
MAPKAPK-2 (D1E11)	Cell Signaling Technology	12155	1:1000
p-MAPKAPK-2 (T334) (27B7)	Cell Signaling Technology	3007	1:1000
PARP	Cell Signaling Technology	9542	1:1000
BCL2	Cell Signaling Technology	4223	1:1000
MCL1	Santa Cruz Biotechnology	sc-819	:1,000
BAX	Cell Signaling Technology	2772	1:1,000
BIM	Cell Signaling Technology	2819	1:1,000
c-Myc	Cell Signaling Technology	5605	1:2000
p27/Kip1	Abcam	ab92741	1:2000
Tubulin	Cell Signaling Technology	2128	1:1,000
GAPDH	Santa Cruz Biotechnology	sc-25778	1:5,000

sTable 2

Reagents for flow cytometry	Company	Catalog number	Usage
APC Annexin V	BD Pharmingen	550474	5 ul per test
SYTOX Green	Life Science	S34860	5 uM final conc.
DCFDA	Invitrogen	D399	1- 10 uM final conc.

sTable 3

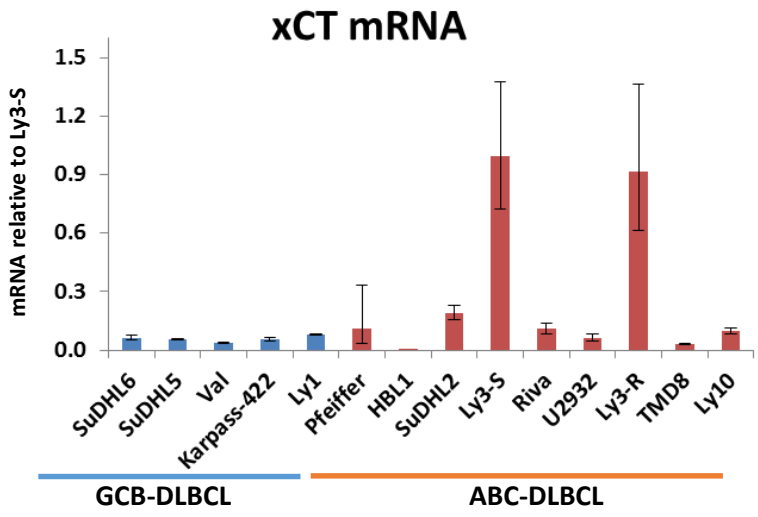
Chemicals	Company	Catalog number
MTT	BD Pharmingen	550474
sulfasalazine	Sigma	S0883
SB203580	SelleckChem	S1076
Glutathione ethul ester (GEE)	Cayman Chemical	14593
Cyclophosphamide	Sigma	C0768
Adriamycin (Doxorubicin)	Sigma	44583
Vincristine	Sigma	V8879
Prednisone	Sigma	P6254

sTable 4

RT-PCR Primers	Sequence
xCT Forward	5' CCTGGCATTTGGACGCTACAT
xCT Reverse	5' TCAGAATTGCTGTGAGCTTGC
HPRT Forward	5' ACCCCACGAAGTGTTGGATA
HPRT Reverse	5' AAGCAGATGGCCACAGAACT
18S rRNA Forward	5' GGCCCTGTAATTGGAATGAGTC
18S rRNA Reverse	5' CCAAGATCCAACTACGAGCTT

Figure S1. (Related to Fig. 1)

A.



B.

COO subtype	Cell line	SASP IC50 (nM)
GCB	SuDHL5	450
	Val	940
	Karpass-422	1600
	Pfeiffer	500
ABC	HBL1	750
	SuDHL2	750
	Ly3-S	780
	Riva	900
	TMD8	400

t-test, GCB vs ABC, p = 0.555

C.

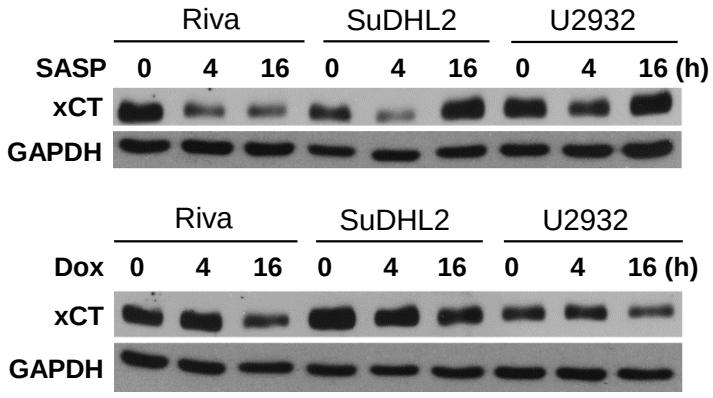


Figure S1. **xCT expression analysis and sensitivity of DLBCL cell lines to SASP**.
(**A**) xCT mRNA expression in a panel of 14 DLBCL cell lines. Plotted values are relative to that in Ly3-S, which is set as 1.0.
(**B**) SASP IC50 values in 9 DLBCL cell lines based on 48 hr MTT assays.
(**C**) xCT protein levels in Riva, SuDHL2, and U2932 cells treated with SASP (top) and Dox (bottom) for the indicated amount of time.

Figure S2. (Related to Fig. 2)

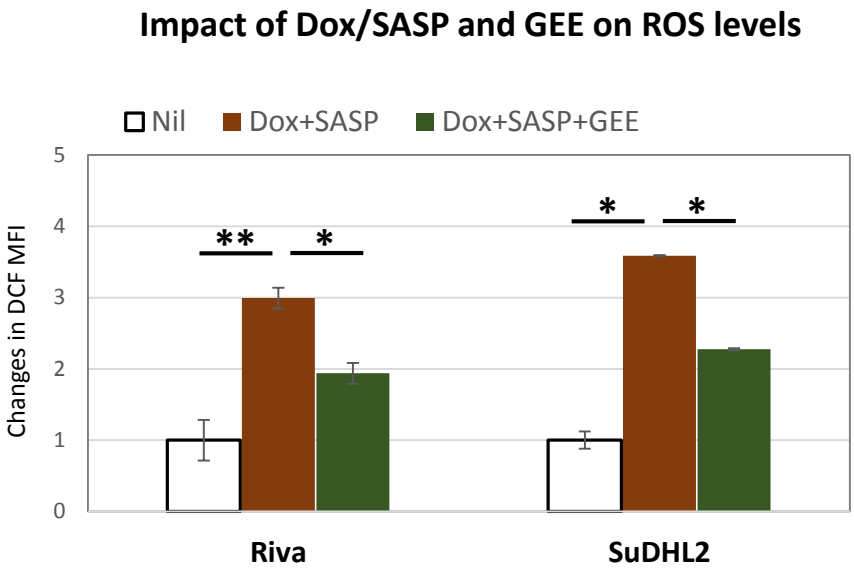


Figure S2. **Exogenous GEE blunted ROS surge triggered by DOX/SASP combination**. ROS (DCF) levels in Riva and SuDHL2 cells treated with either DMSO or Dox/SASP combination with and without the GEE pretreatment step. GEE was used at 1 mM. Both Dox and SASP were used at IC50 doses.

Figure S3. (Related to Fig. 3)

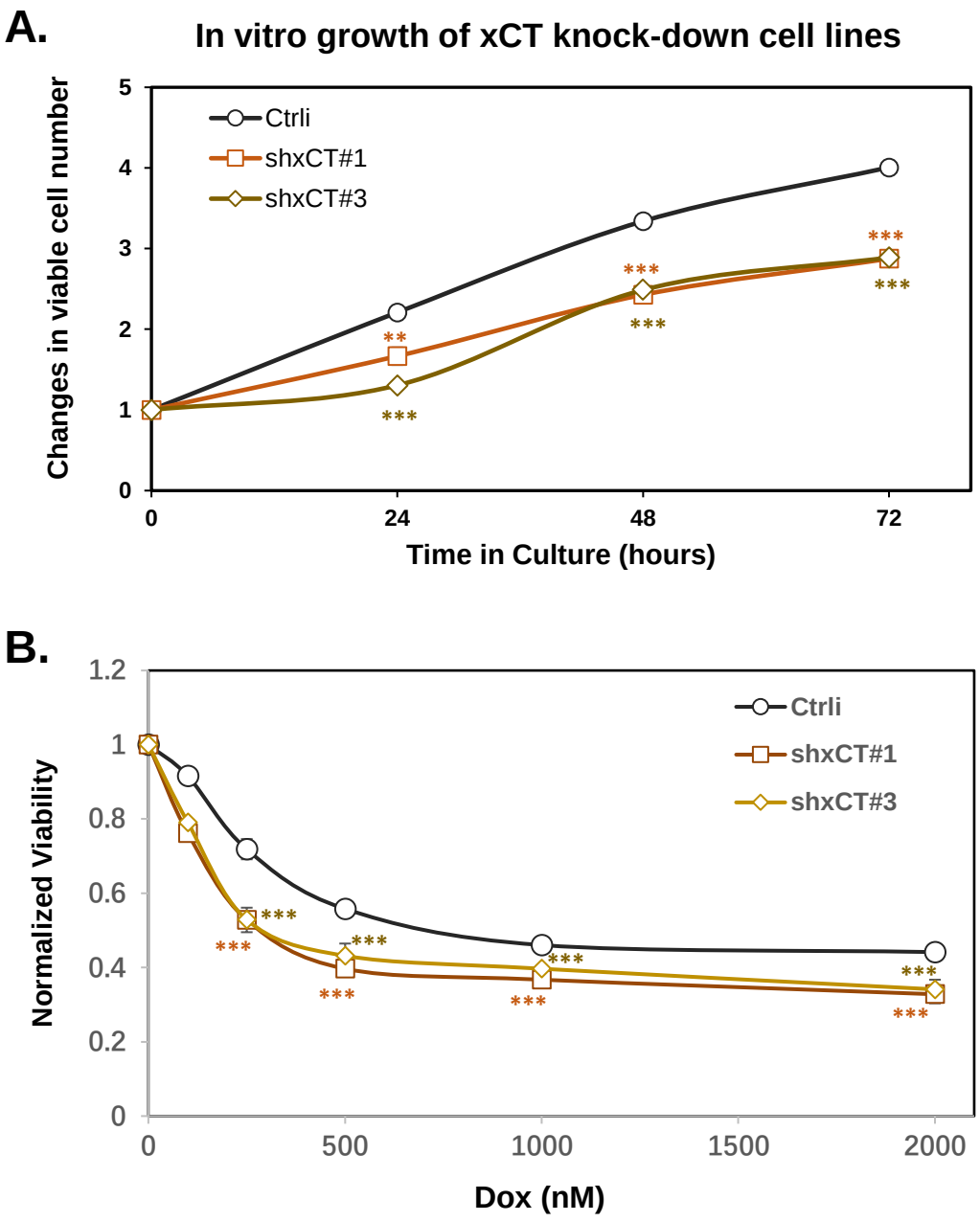


Figure S3. **Stable xCT knock-down in Riva cells decreased in vitro proliferation capacity (A) and increased sensitivity to Dox treatment (B)**.
T-tests were used to compare the xCT KD cell lines with the Ctrli sample. **, $p < 0.01$, ***, $p < 0.001$.

Figure S4. (Related to Fig. 4)

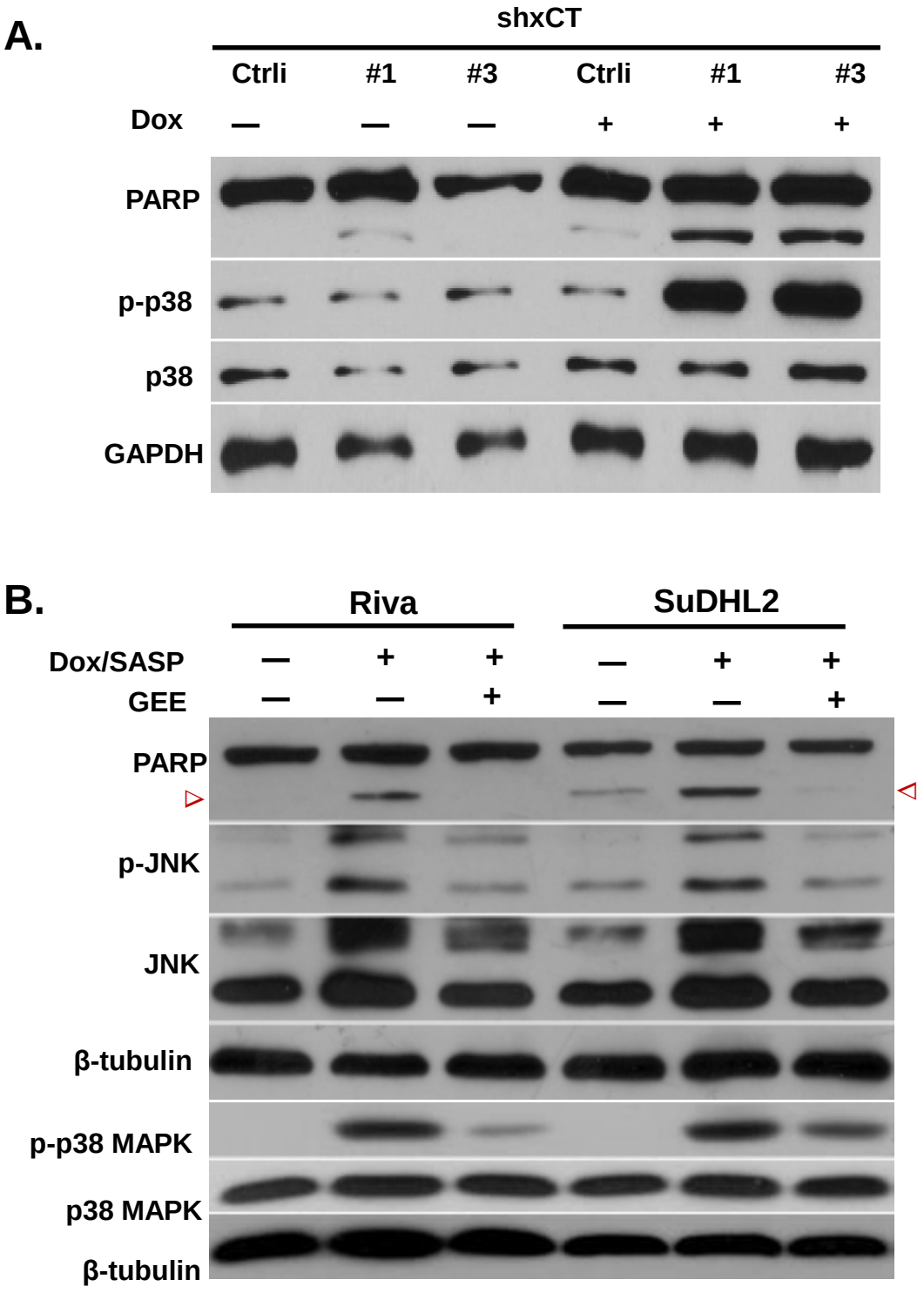


Figure S4. **Impact of xCT KD, Dox/SASP treatment, and GEE on p38 and JNK Signaling.** (**A**) p38 activation status in Riva xCT KD cell lines with and without Dox treatment. (**B**) p38 and JNK activation status following Dox/SASP treatment with and without GEE pretreatment.

Figure S5. (Related to Fig. 6)

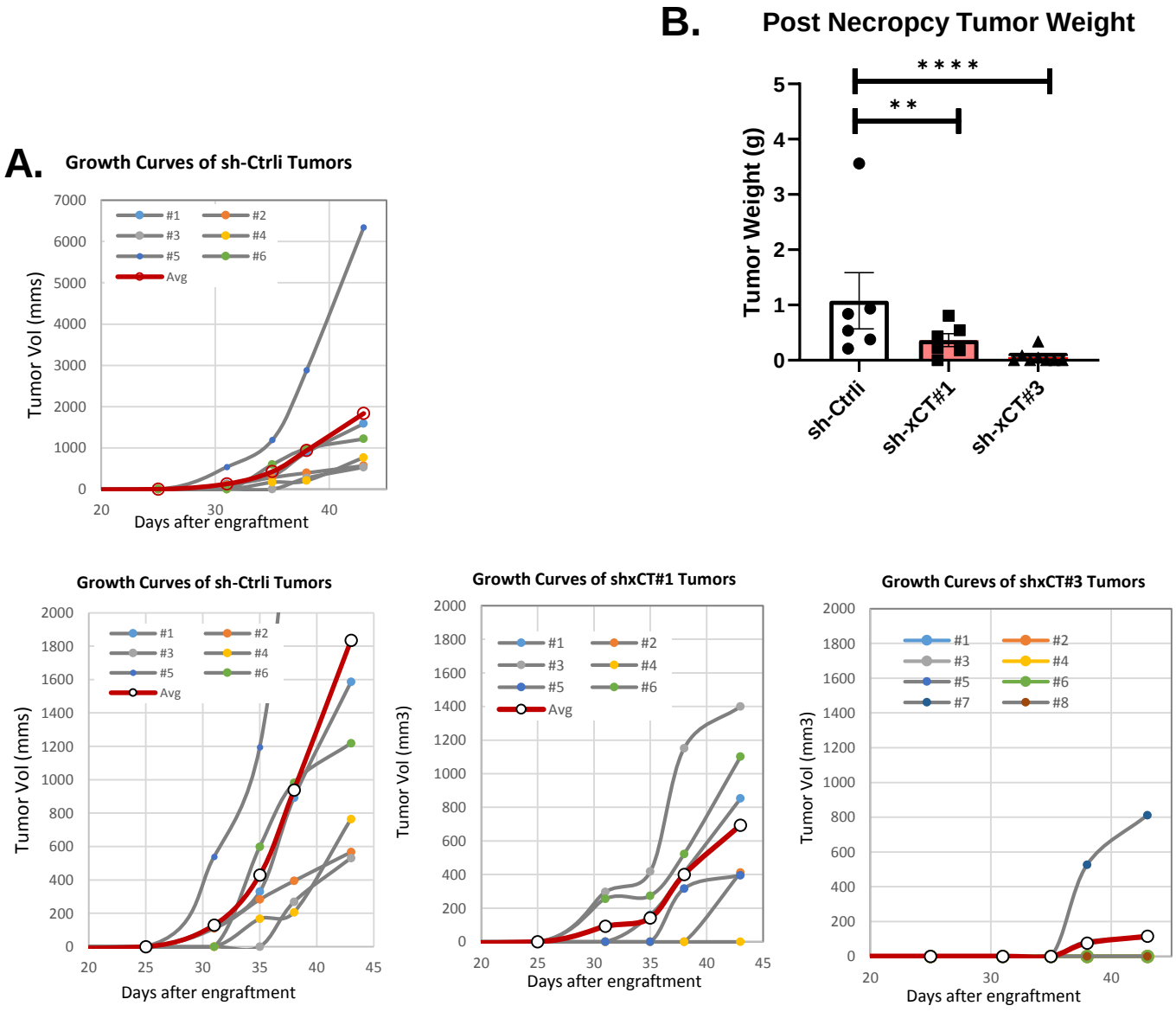


Figure S5. **Genetic inactivation of xCT retarded in vivo growth potential of Riva cells in NSG mice.**

(**A**) Growth curve of individual tumors. The top and the left panel in the second row are the same result but presented with different Y-axis scale. The middle and right panel represent shxCT#1 tumors and shxCT#2 tumors. Bold and red lines represent group mean in each graph.

(**B**) Weight of individual tumors were recorded after necropsy on day 43. 2-tailed t-tests were performed to compare tumors arising from the KD stable lines to those from the Ctrli genotype. **, $p < 0.01$, ***, $p < 0.001$.