Supplemental Figure legends:

FIGURE S1. Antibody mediated depletion of CD4+ T cells in C57BL6/J treated with CCl_4. (**A**) Antibody mediated CD4+ T cell depletion: days -1, and day 0 mice were administered 0.5mg of anti-CD4 (Clone GK1.5) I.P. and CCl_4 treatment beginning day 0, every three days- 12 doses per animal. On days 14 and 28, animals were administered anti-CD4 I.P. (**B**) Representative FACS plots of antibody mediated CD4 depletion in liver (top) and spleen (bottom) at time of animal sacrifice, blood was monitored throughout the study as indicated in the methods section (data not shown). Data are representative of at least 3 independent experiments with 3-5 animals per indicated group. Gated on live non-autofluorescent CD3+ (T cell compartment). (**C**) Mouse livers were processed for liver non-parenchymal cells (NPCs) isolation as described in Materials and Methods. After density gradient enrichment, NPCs were stained with anti-CD45 and analyzed on a FACSAria Cell Sorter II (BD Bioscience) equipped with a UV laser. HSCs were identified as Live, UV autofluorescence-positive (UVAF+), CD45 negative population. For the detection of HSC-associated activation marker, purified liver cells were stained intracellularly with α-SMA. The expression of α-SMA was analyzed on gated HSC population using FlowJo software (Treestar, Ashland, OR). Data shown is representative of 3 independent experiments (n=3-5 mice per group). ***$p<0.0005$, two-tailed Mann-Whitney *U* test. Where applicable, error bars represent SEM.

FIGURE S2. CCl_4 treatment primarily alters the hepatic B cell compartment. (**A**) Spontaneous IgG production from splenic lymphocytes; ELISPOT was performed as described. (**B**) Comparison of fibrotic liver (795±291 ASC/10^6) versus animal-matched splenic (342±137 ASC/10^6) frequencies of spontaneous IgG production. All data are representative of three independent experiments, n=3-5 animals per group. Statistical significance was determined by two-tailed Mann-Whitney *U* Test, ***$p<0.005$.

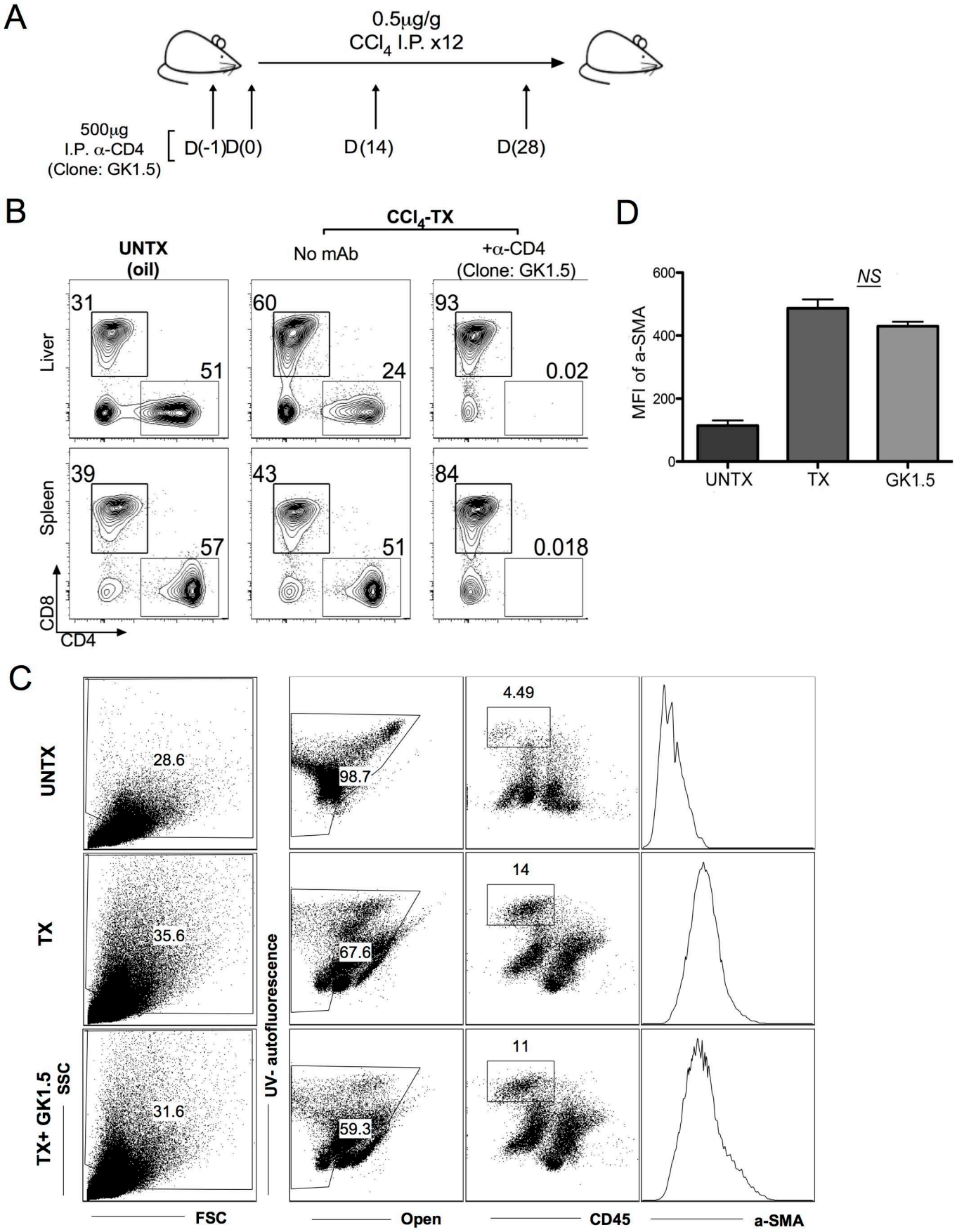
FIGURE S3. Increased B cell activation and survival during liver fibrosis. (**A)** Phenotypic analysis of live, non-autofluorescent, CD19+ B cells from non-fibrotic (UNTX) and fibrotic (TX) livers; left. Right, analysis of Ki-67 and CD44 expression directly *ex vivo* within the CD95+ IgD- population. Fibrotic liver B cells have an increased frequency of CD95+IgD- B cells in comparison to non-fibrotic controls, far right (***p<0.0005, two-tailed Mann-Whitney *U* Test). Each dot represents one mouse; data shown are from 3 independent experiments, n=3-5 animals per group. **(B)** Direct *ex vivo* analysis of apoptosis via positive staining for Annexin-V and Propidium Iodide (PI) on hepatic CD19+ B cells. Gates were determined from single stained positive and negative controls. FACS plots and graphs are representative of 2 independent experiments, n =3-5 per group (***p<0.0005, two-tailed Mann-Whitney *U* Test).

FIGURE S4. CD25 negative CD4+ T cell interaction with B cells is not influenced by fibrosis. (**A**) Foxp3 expression on bead-enriched CD4+CD25+ T cells, representative of indicated organs from 5 independent experiments (pooled cells from n=3-5 per group). (**B**) Total CD4+ T cell compartment expression of CD25 and Foxp3 prior to depletion of CD25+ fraction (top), and Foxp3 expression in CD25 negative fraction of CD4+ T cell compartment (bottom) prior to co-culture with B cells. Data representative of 5 independent experiments of pooled organs from n=3-5 animals per group (**C**) Ki-67 and CD44 co-expression on live, B220+ B cells following 5 days of stimulation with 2 μg/mL LPS and indicated CD4+ T cells. Total CD4+ T cells from spleen and untreated liver reduce expression of activation markers, while fibrotic liver permits activation (left, top). CD25-depleted fraction permits B cell activation to the same extent irrespective of origin. Statistical significance is relative to B cell activation with LPS in the absence of CD4+ T cells (***p<0.0005, two-tailed Mann-Whitney *U* Test). (**D**) IgG production from B cells cultured with total CD4+ T cell

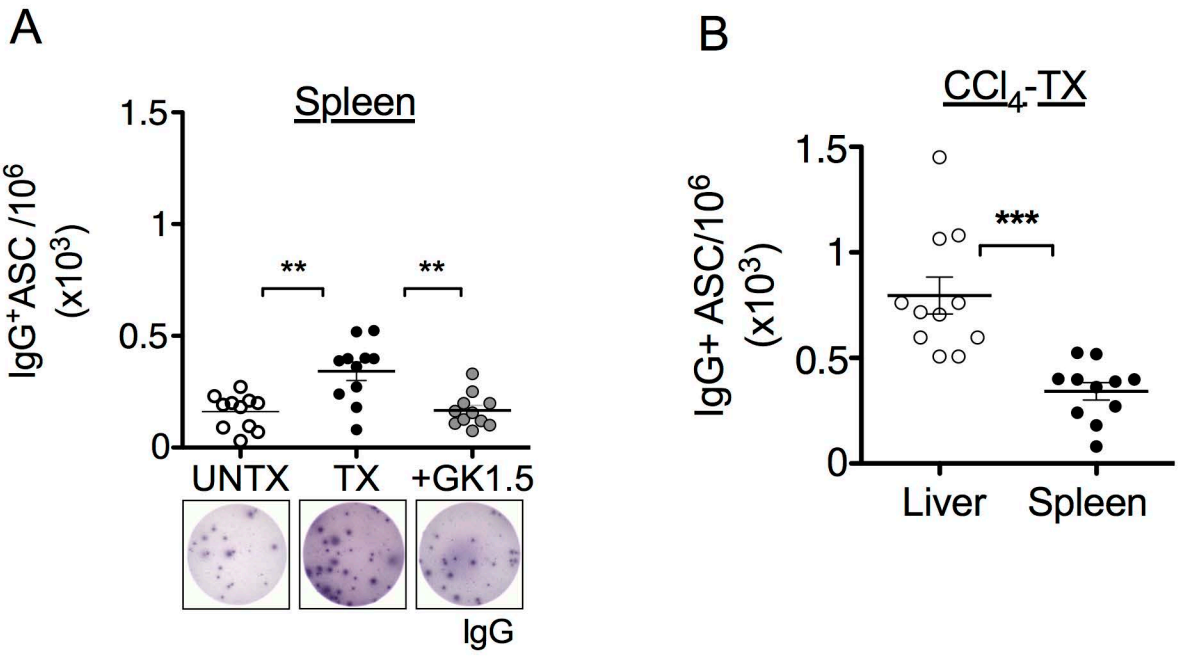
compartment (top) and CD25-depleted fractions (bottom). All data are representative of at least 5 independent experiments with indicated cell populations pooled from n=3-5 animals per group. Statistical significance is relative to B cell activation with LPS in the absence of CD4+ T cells (**p<0.005, *p<0.05, two-tailed Mann-Whitney *U* Test). Where applicable, error bars represent SEM.

FIGURE S5. Phenotypic analysis of splenic CD4+Foxp3+ cells. (**A**) Representative FACS plots of splenic CD4+ T cell phenotype showing CD69, PD-1 and CD40L expression. Gated on live, non-autofluorescent, CD4+ T cells. (**B**) Total CD4+ T cell compartment expression of CXCR5 and ICOS; Foxp3+ population represented on top panel, Foxp3- population represented on bottom panel. All data are representative of at least 3 independent experiments (n=3-5 animals per group).

FIGURE S6. Intrahepatic accumulation of CD4+Foxp3+ T cells and incidence of spontaneous IgG production are independent of HCV viral load. (**A)** Intrahepatic frequency of CD4+Foxp3+ T cells does not correlate with patient viremia (n=15), R= -0.18 (Spearman), p=0.52 (two tailed, *NS*). (**B)** Spontaneous IgG production by intrahepatic B cells does not correlate with patient viremia (n=15), R= -0.06 (Spearman), p=0.82 (two tailed, *NS*).



Supplementary Fig. S1



Supplementary Fig. S2.

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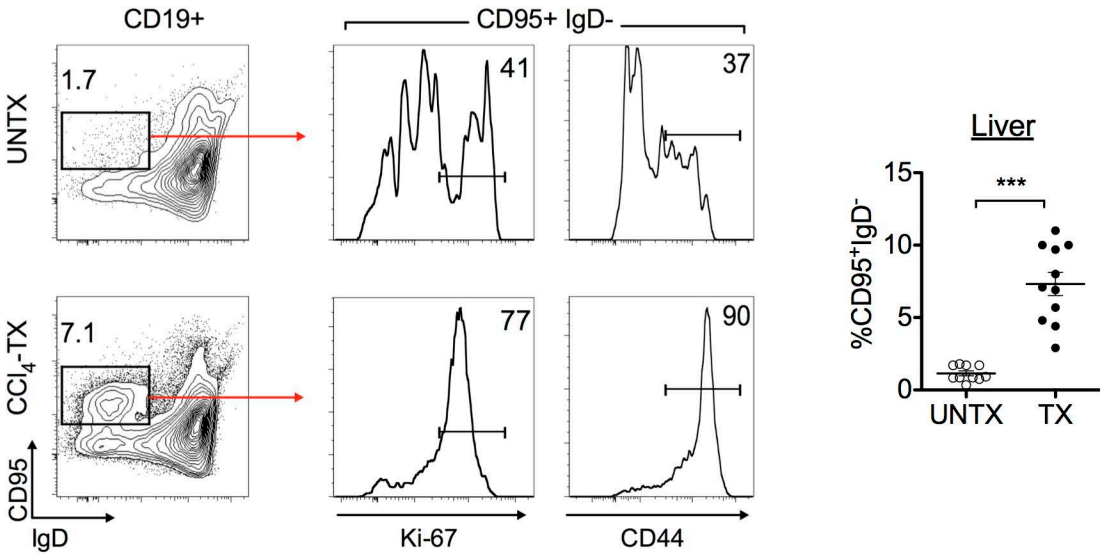

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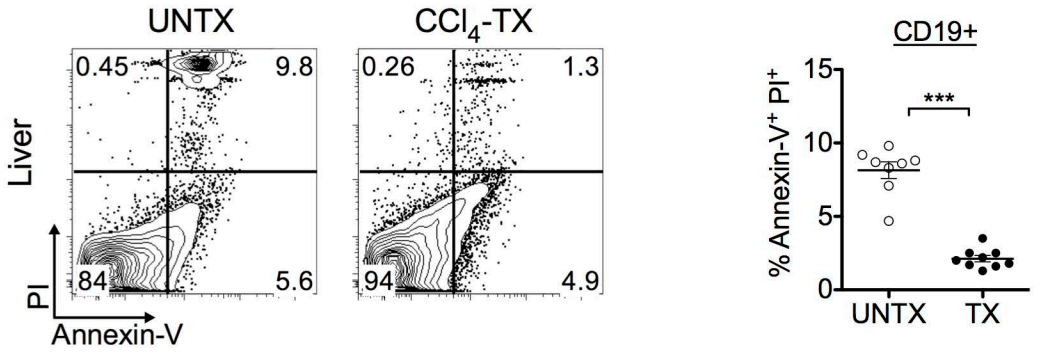

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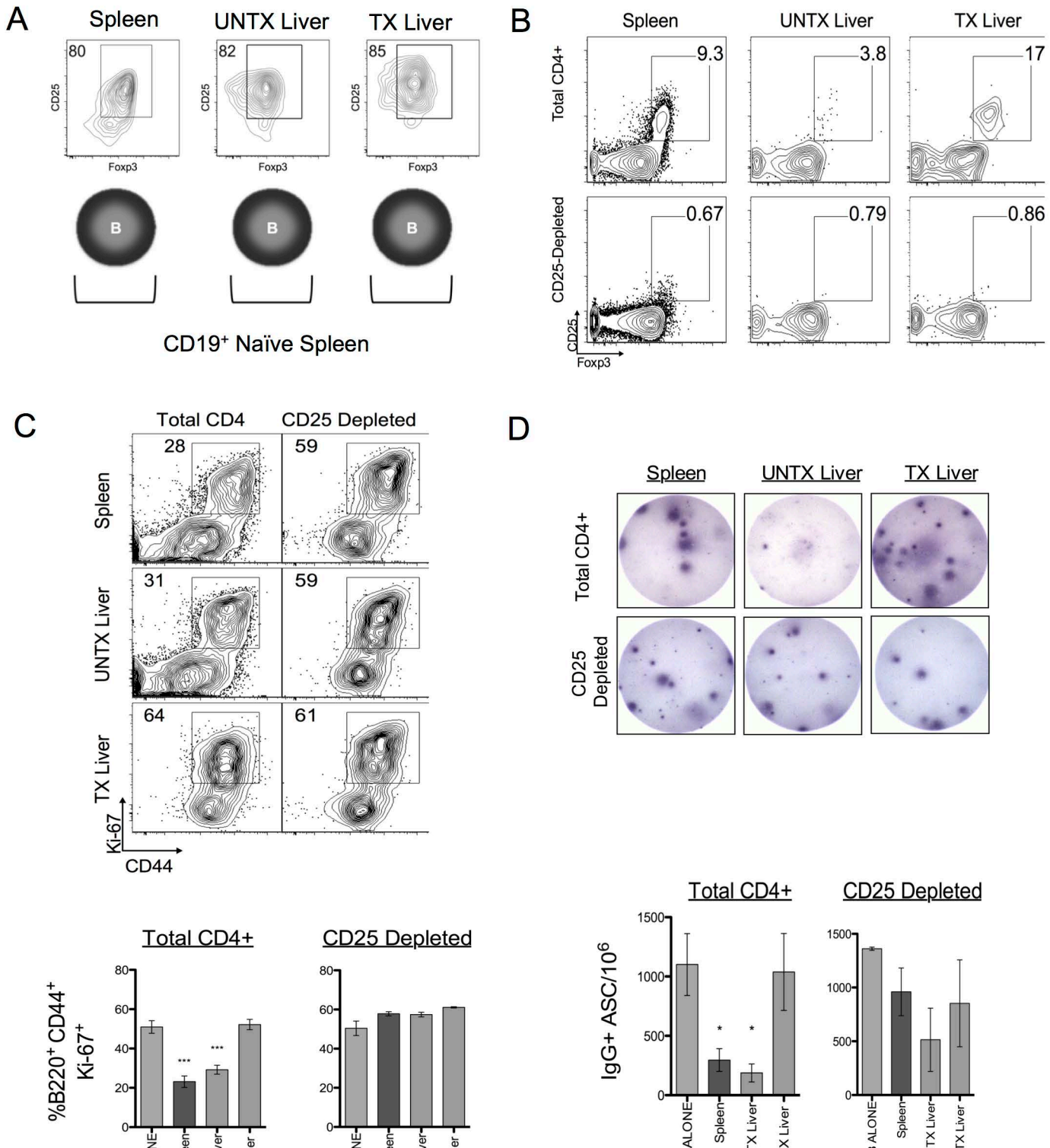

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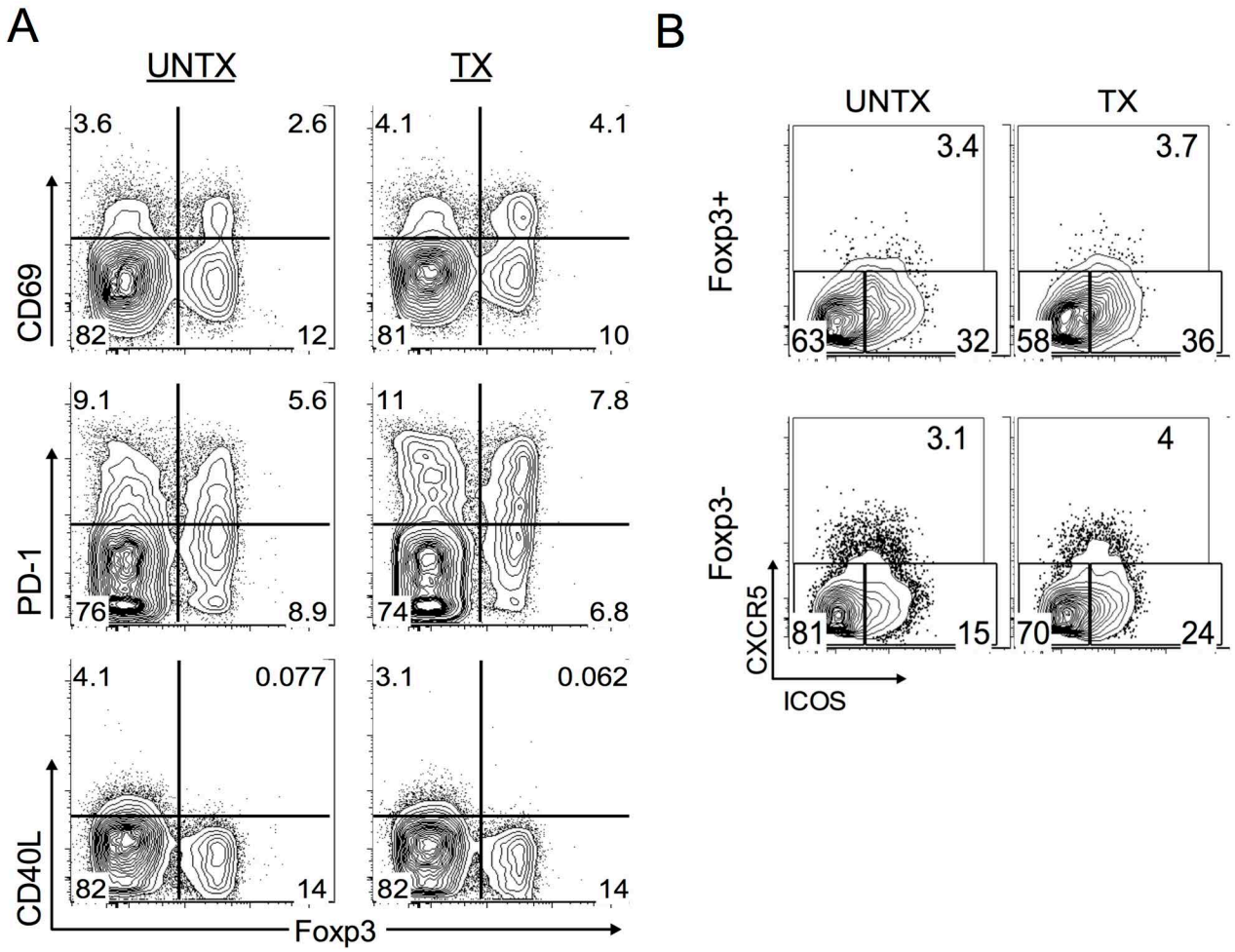

Supplementary Fig. S5.

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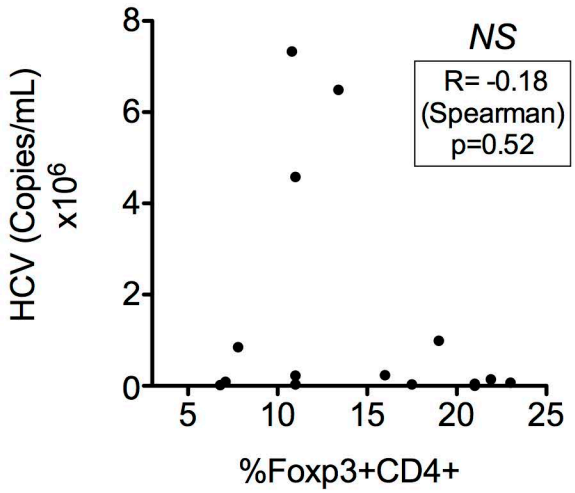

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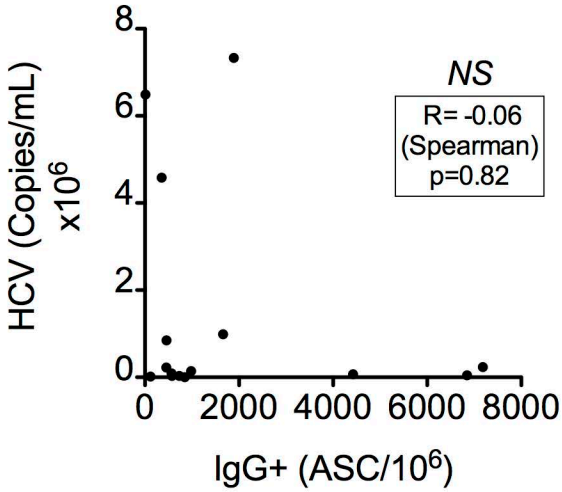

Supplementary Fig. S6.

Fibrosis Lesion Scoring (adapted from Ishak, et al. J Hepatology 1995; 22:696-9)

Ishak Stage, Categorical description	Score
No fibrosis	0
Expansion of some portal areas with or without short fibrous septa	1
Expansion of most portal areas with or without short fibrous septa	2
Expansion of most portal areas with occasional portal to portal bridging	3
Expansion of portal areas with marked bridging (portal-portal and/or portal-central)	4
Marked bridging with occasional nodules	5
Cirrhosis, probable or definitive	6

Histopathological Evaluation and Fibrosis Lesion Quantification

Animal ID	Slide ID	H&E	Sirius red-Fibrosis score
Group 1	1 C	NSF*	0
	2 C	NSF	0
	3 C	NSF	0
	4 C	NSF	0
	5 C	NSF	0
Group 2	1 Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	2 Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	3 Tx	Multifocal extensive areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	4 Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	5 Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
Group 3	1 GK+Tx	Multifocal extensive areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	2 GK+Tx	Multifocal extensive areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	3 GK+Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	4 GK+Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3
	5 GK+Tx	Multifocal moderate areas of hepatocellular necrosis, hydropic degeneration, periportal fibrosis with occasional portal to portal bridging and occasional mononuclear to neutrophilic infiltrates	3

* NSF: no significant findings; C: oil-treated control, Tx: CCl4-treated, and GK+Tx: CCl4+ GK1.5 antibody treated.

Donor ID	Age	Sex	Cirrhosis	Dx	HCC	HCV RNA (Copies/mL)	ALT
ET101	48	M	YES	HCV	YES	80000	42
ET104	53	M	YES	HCV	YES	7330000	137
ET108	60	M	YES	HCV	YES	233000	45
ET180	63	M	YES	HCV	YES	68700	42
ET196	70	M	YES	HCV	NO	31500	29
ET239	57	M	YES	HCV	YES	3400	27
ET245	47	M	YES	HCV	YES	46900	37
ET261	66	M	YES	HCV	YES	4580000	93
ET262	61	F	YES	HCV	NO	847000	71
ET264	53	F	YES	HCV	NO	225000	30
ET303	67	M	YES	HCV	YES	16300	99
ET308	60	M	YES	HCV	YES	989000	38
ET316	66	F	YES	HCV	YES	44600	26
ET330	50	M	YES	HCV	YES	30400	28
ET334	49	M	YES	HCV	YES	1420000	64
ET371	59	M	YES	HCV	YES	Undet*	30

Supplementary Table 2. Clinical characteristics HCV patients in this study. Explanted cirrhotic liver tissues from HCV infected patients undergoing orthotopic liver transplantation were obtained following informed written consent. Abbreviations: Dx= diagnosis; Undet= undetectable plasma viral load; HCV= hepatitis C virus; HCC= hepatocellular carcinoma; ALT= alanine aminotransferase. Asterisk (*) indicates that donor was treated for HCV infection with PEG-IFNa/Ribavirin course prior to liver transplant.

Donor ID	Age	Sex	Cirrhosis	HCV	HCC	Dx	ALT
ET195	42	M	NO	NEGATIVE	NO	Resection/ Cholangiocarcinoma	35
ET203	42	F	NO	NEGATIVE	NO	Resection/ Hemangioendothelioma	30
ET222	40	M	NO	NEGATIVE	NO	Resection/ Cholangiocarcinoma	45
ET321	24	M	NO	NEGATIVE	NO	Resection/ Negative	32
ET322	Unknown	Unknown	NO	NEGATIVE	NO	Donor liver, resectioned to accommodate pediatric recipient	Unknown
ET331	47	M	NO	NEGATIVE	NO	Resection/ Negative	38

Supplementary Table 3. Clinical characteristics non-fibrotic control subjects in this study. Liver tissues were obtained following informed written consent from patients undergoing surgical re-sectioning for non-HCV, non-NAFLD, non-ALD related medical treatments or re-sectioned donor liver to accommodate pediatric recipient. Livers were considered non-fibrotic as medical staff did not diagnose cirrhosis in these specimens. Abbreviations: Dx= diagnosis; HCV= hepatitis C virus; HCC= hepatocellular carcinoma; ALT= alanine aminotransferase.