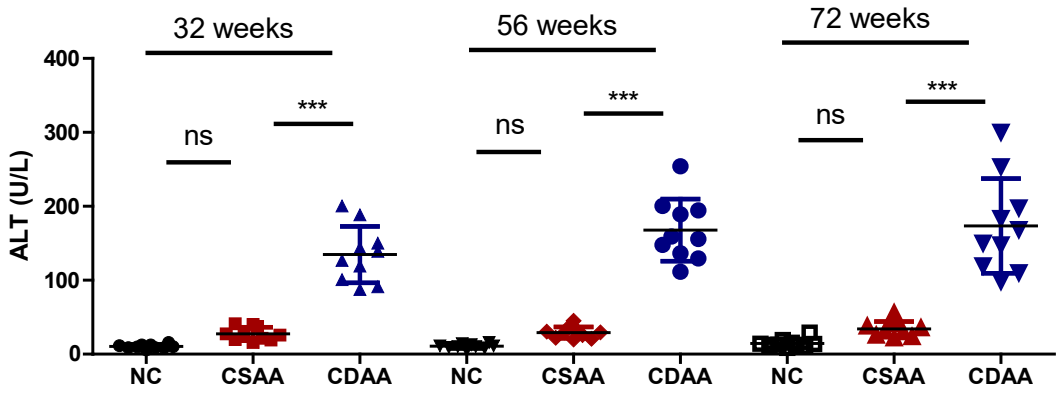
Supplemental Information

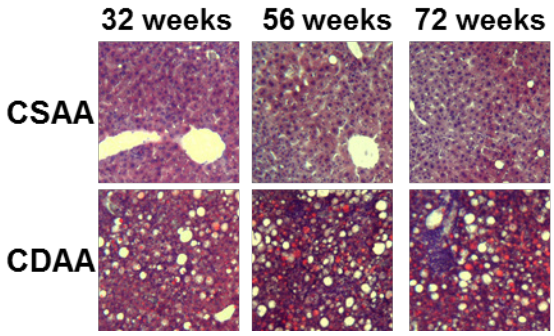
Supplemental Figure 1

Serum ALT level in mice. Mice fed with CDAA diet showed significantly higher levels of serum ALT activities compared with mice fed with CSAA diet or normal chow (NC) (***p<0.001)



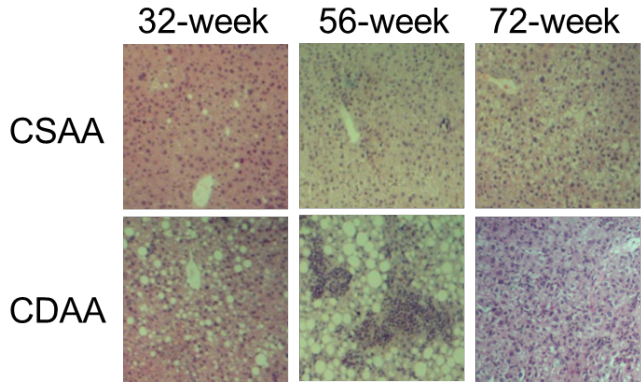
Supplemental Figure 2

Oil Red O staining on liver sections. Mice fed with CDAA diet exhibited significant accumulation of lipid droplets in the liver.



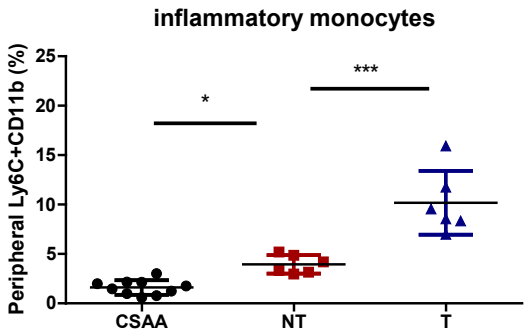
Supplemental Figure 3

H&E staining of liver section of CSAA and CDAA diet-fed mice. Mice fed with CDAA diet for 56 and 72 weeks showed marked microscopic features of tumor lesions.



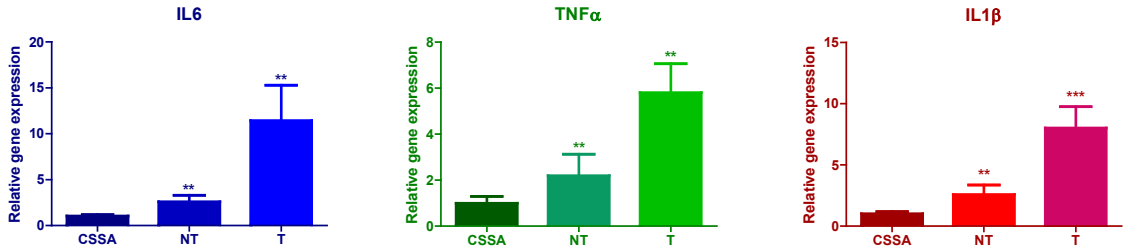
Supplemental Figure 4

Mice with hepatic tumors exhibited a significantly higher level of liver inflammation as well as inflammatory monocytes in the peripheral blood. Circulating mononuclear cells in mice with fed with CSAA or CDAA diet for 56-weeks were analyzed with flow cytometry. CDAA diet-fed mice were sub-grouped according to the condition of their tumors (n=5per group). Mice with tumors exhibited higher levels of inflammatory monocytes in peripheral blood (*p<0.05, ***p<0.001)



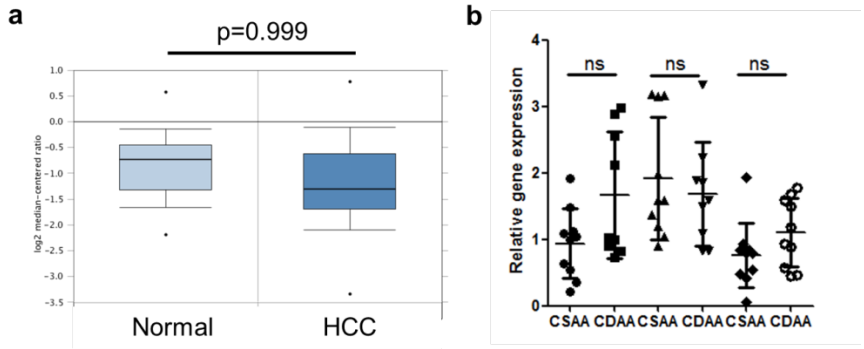
Supplemental Figure 5

Intensive apoptosis in hepatocytes following transcriptional activation of inflammatory genes in the peritumour region. Livers from CSSA diet-fed mice (CSSA) and CDAA diet-fed mice without hepatic tumors (NT), and with hepatic tumors (T) were collected and RNA was isolated. Expression of inflammatory genes was measured by qRT-PCR. (**p<0.01, ***p<0.001)



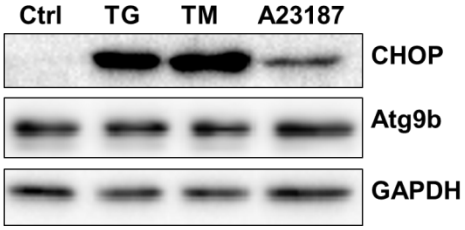
Supplemental Figure 6

LC3 was not transcriptionally regulated during hepatic carcinogenesis. **a**) LC3B was not down-regulated in HCC. Data and image were collected from Oncomine with human normal liver=76 and HCC=104. LC3B expression had no significant difference between the two groups. **b)** mRNA expression of LC3B was not significantly suppressed in hepatocytes from mice fed with CDAA diet.



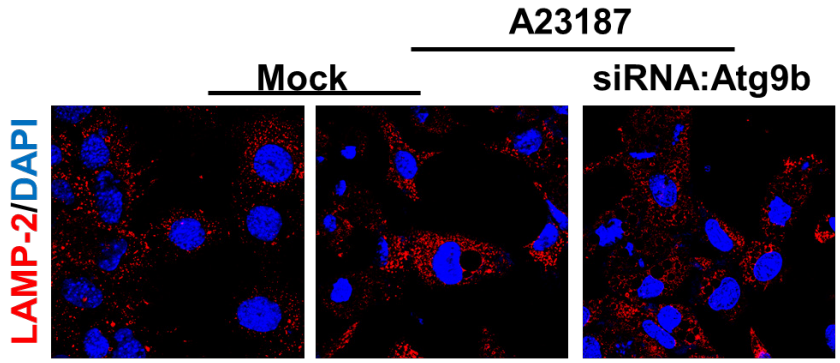
Supplemental Figure 7

ER stress did not induce expression of Atg9b in hepatocytes. AML12 cells were treated with vehicle, 1μM TG, 5μM or 0.5μM A23187 for 6 hours, and expression of CHOP, ER stress maker, and Atg9b were determined by immunoblotting.



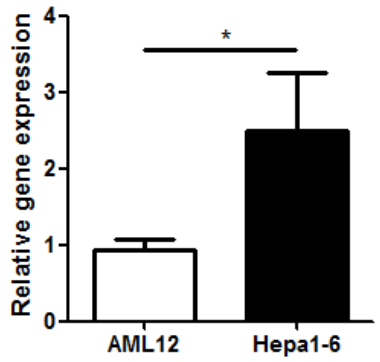
Supplemental Figure 8

RNA interference against Atg9b did not alter the expression or cellular localization of LAMP-2. AML12 cells were treated with scramble negative control (Mock) or siRNA against Atg9b. 48 hours after RNAi, cells were treated with either vehicle or 0.5µM A23187 for 6 hours. Expression and localization of LAMP-2 were determined by immunofluorescence.



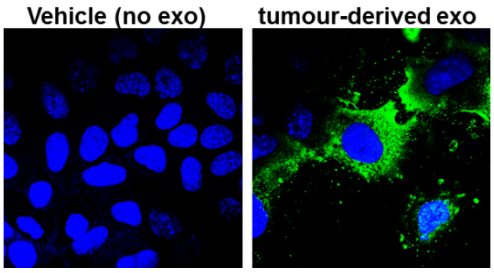
Supplemental Figure 9

Expression of miR-3091-3p was higher in murine liver cancer cell line. RNA was collected from murine hepatocyte cell line AML12 and murine liver cancer cell line Hepa1-6. qRT-PCR analysis revealed that expression of miR-3091-3p in Hepa1-6 cells was higher than AML12.



Supplemental Figure 10

Internalization of tumour-derived exsosomes. AML12 hepatocytes could internalize Hepa1-6 cells-derived exosomes.



Supplemental Table 1

Descriptive analysis of liver specimens from mice.

	Age, week	B.W.	Tumour incidence (%)	Number of observable nodules	LW/BW (%)
CSAA	**56**	**41.9±6.8**	**0/10(0)**	**0**	**4.31%±0.66%**
CDAA	**56**	**39.9±6.2**	**5/10(50)**	**1.7±1.4**	**6.00%±1.70%**
CSAA	**72**	**48.2±2.9**	**0/10 (0)**	**0**	**4.79%±0.47%**
CDAA	**72**	**45.8±3.5**	**10/10 (100)**	**5.7±1.6**	**10.84%±1.68%**

Supplemental Table S2

Subsets of miRNAs that were upregulated or downregulated in Non-tumor livers (NT) or tumoral livers (T) of CDAA diet-fed mice

Items	miRNAs
Downregulated genes	
T v.s. NT	mmu-let-7a-2-3p, mmu-miR-200a-3p, mmu-miR-142-5p, mmu-miR-143-3p, mmu-miR-142a-3p, mmu-miR-199a-3p, mmu-miR-199a-5p, mmu-miR-199b-3p, mmu-miR-199b-5p, mmu-miR-145a-3p, mmu-miR-145b, mmu-miR-1957a, mmu-miR-491-3p, muu-miR-141-3p, mmu-miR-125b-5p, mmu-miR-139-5p
Upregulated genes	
T v.s. NT	mmu-miR-677-3p, mmu-miR-466n-3p, mmu-miR-185-3p, mmu-miR-31-5p, mmu-miR-346-3p, mmu-miR-1971, mmu-miR-2137, mmu-miR-592-3p