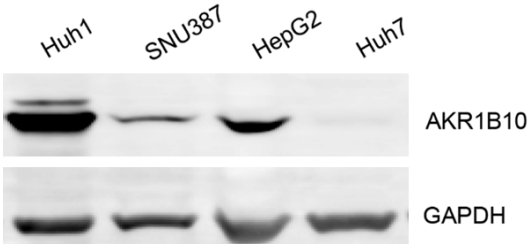
Supplementary Table 1. Summary of oligo nucleotides sequences for constructing AKR1B10-shRNA plasmids

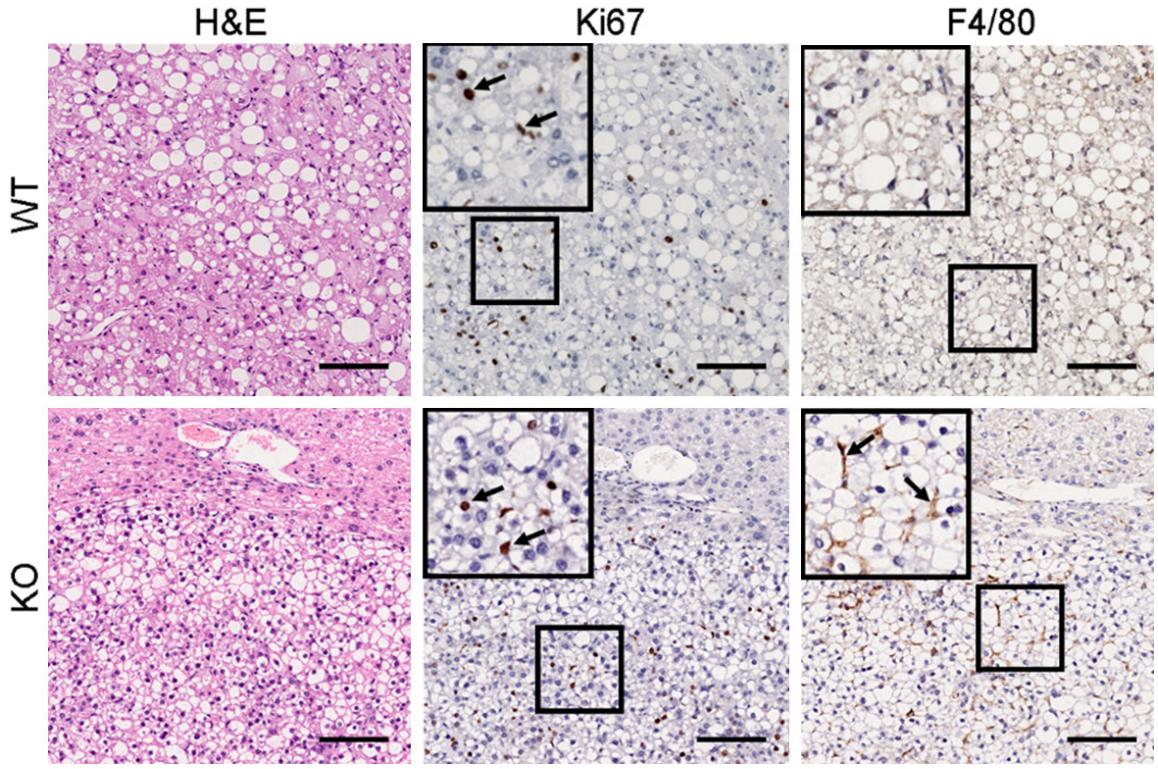
Oligos	Sequences
AKR1B10-sh1+	5'-GATCCGCAAGTGTGACTACCTCCACTCATTCAAGAGATGAGTGGAGGTAGTCACACTTTTTTTG-3'
AKR1B10-sh1-	5'-AATTCAAAAAAAGTGTGACTACCTCCACTCATCTCTTGAATGAGTGGAGGTAGTCACACTTGCG-3'
AKR1B10-sh2+	5'-GATCCGCAAGATCACAGTGAACTTAGTCTTCAAGAGAGACTAAGTTCACTGTGATCTTTTTTTG-3'
AKR1B10-sh2-	5'-AATTCAAAAAAAGATCACAGTGAACTTAGTCTCTCTTGAAGACTAAGTTCACTGTGATCTTGCG-3'

Supplementary Table 2. Primer sets for constructing luciferase-related plasmids

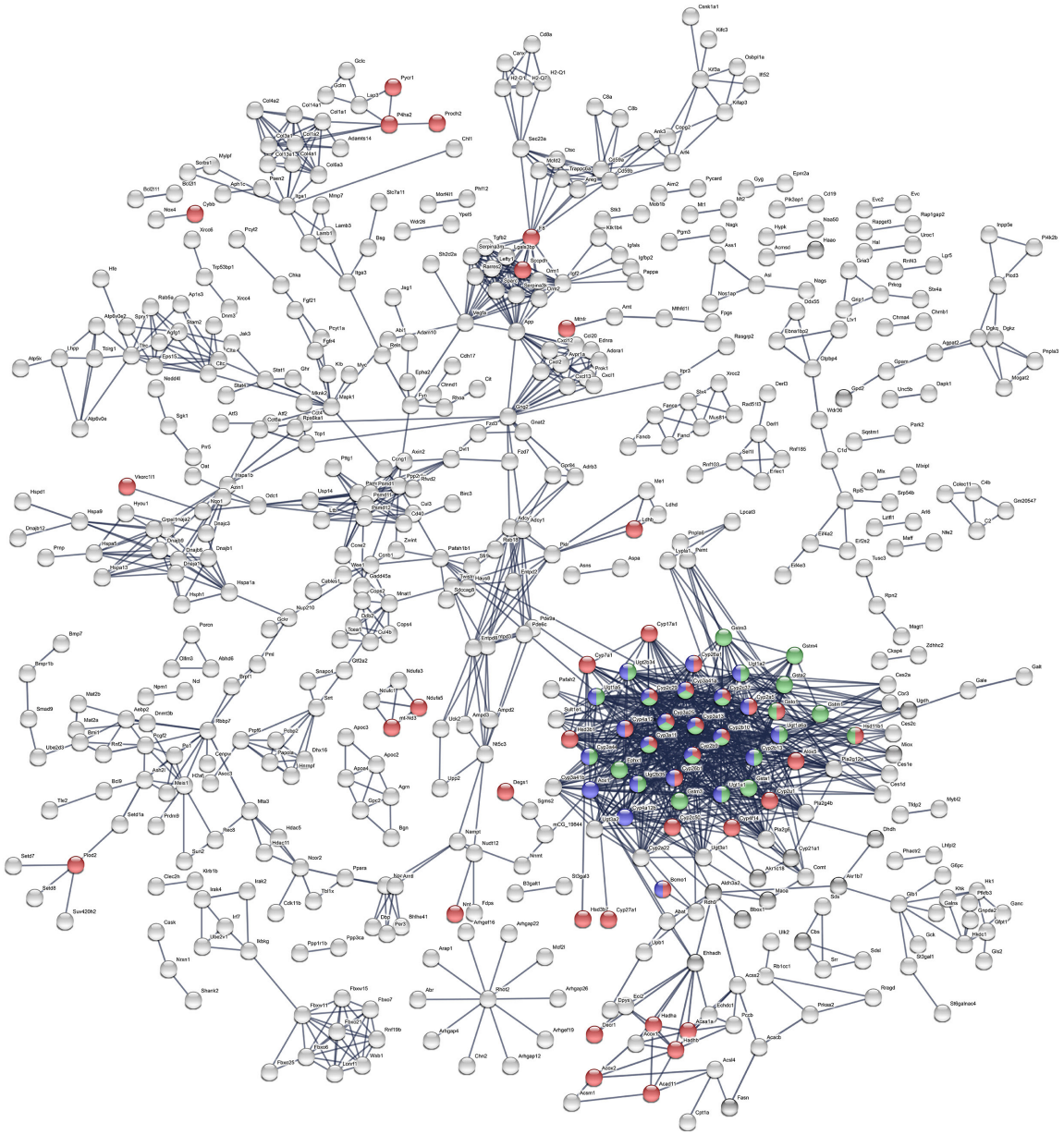
Primer name	Sequences
AKR1B10-luc-F	Forward: 5'-CGGGGTACCAGATTCAACCAAAGCCAACTCATC-3'
AKR1B10-luc-R	Reverse: 5'-CCGCTCGAGGTAGAAGTCTCACGTCCTGCTCTC-3'
AKR1B10-luc-M-F	Forward: 5'-ccaacttttggctgtgttgaattTGAAGAGTGAGCATGaacaagcagaaactccaatgatac-3'
AKR1B10-luc-M-R	Reverse: 5'-gtatcattggagtttctgcttgttCATGCTCACTCTTCAaattcaacacagccaaaagttgg-3'
NRF-cDNA-F	Forward: 5'-CGGGGTACCATGATGGACTTGGAGCTGC-3'
NRF-cDNA-R	Reverse: 5'-CCGCTCGAGCTAGTTTTTCTTAACATCTGGCTTC-3'



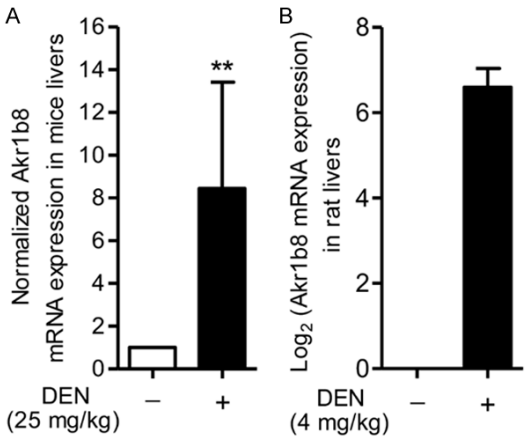
Supplementary Figure 1. AKR1B10 expression assay in four HCC cell lines including Huh1, SNU387, HepG2 and Huh7 by western blot.



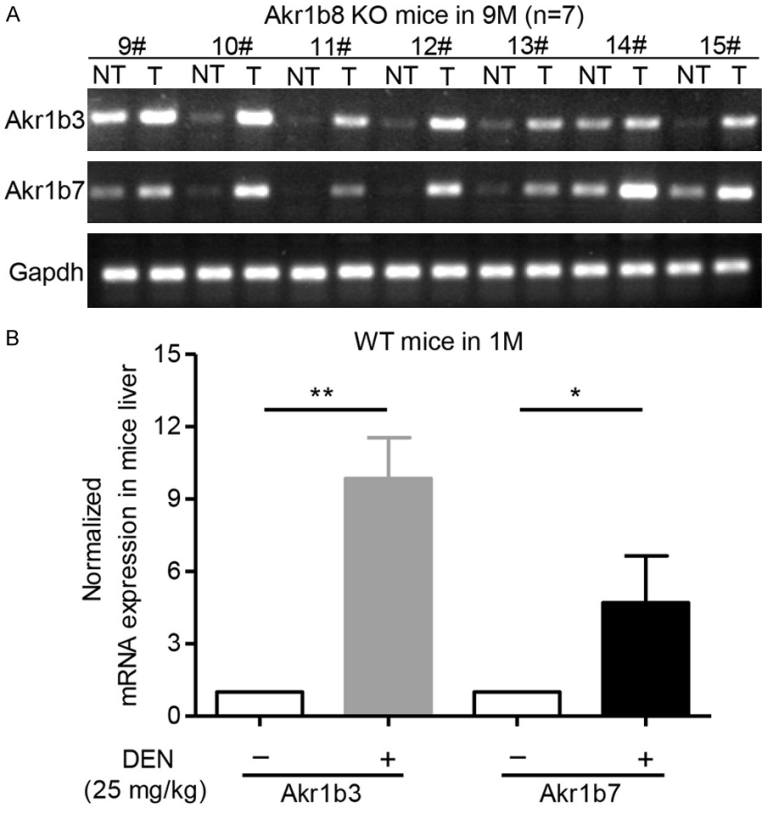
Supplementary Figure 2. H&E staining and IHC of Ki67, F4/80 in Akr1b8 WT and KO mice after 9 months DEN treatment revealed more Kuppfer cells infiltration in the tumor characterized by F4/80 signifying severe inflammatory response status in the Akr1b8 KO mouse livers. H&E staining and IHC of Ki67 indicated the significant HCC development. The insets were high-magnification views. The arrows indicated positive staining. The scale bar is 100 μm.



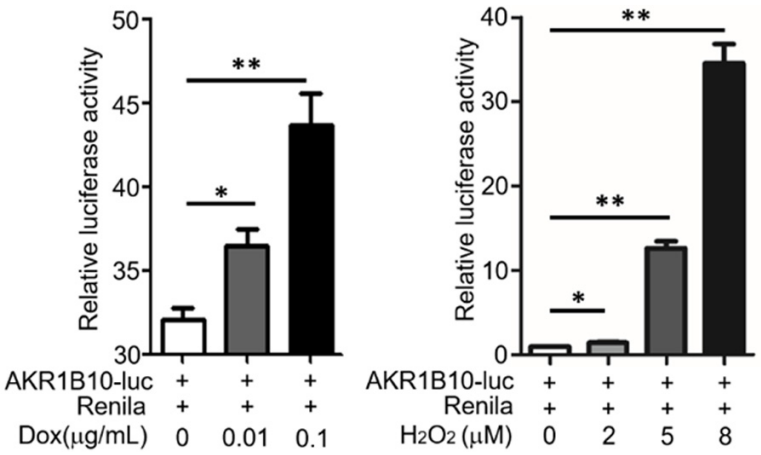
Supplementary Figure 3. Gene relative correlation network among the differently expressed genes in Akr1b8 WT and KO liver tumors after 12 months DEN administration. The gene correlation network was depicted by the STRING database. Genes enriched in oxidoreductase activity, chemical carcinogenesis and retinol metabolism were indicated by red, blue and green color, respectively. The genes with more than one color indicated they were involved in different GO terms or KEGG pathways.



Supplementary Figure 4. Akr1b8 expression assay in mouse or rat livers with or without DEN administration. A. Akr1b8 mRNA expression assay in WT mice livers with (n=5) or without (n=6) DEN administration for 1 months by RT-qPCR. The mice were administrated with DEN at 25 mg/kg. Data shown are the mean ± s.d. (*P<0.05, **P<0.01, Student's t-test, two-sided). B. Akr1b8 mRNA expression assay using the data of whole transcript array on rat livers with (n=3) or without (n=3) DEN administration for 3 months from GEO database (ID: GSE123408). Data shown are the mean ± s.d.



Supplementary Figure 5. The expression of another two members Akr1b3 and Akr1b7 in aldo-keto reductase superfamily in mice. A. Akr1b3 and Akr1b7 expression assays by RT-PCR in tumors (T) and matched non-tumor liver tissues (NT) in Akr1b8 KO (n=7) mice after DEN administration for 9 months. B. Akr1b3 and Akr1b7 expression assays in Akr1b8 WT mice livers upon DEN administration by RT-qPCR. The mice were treated with (n=5) or without (n=6) DEN for 1 month (*P<0.05, **P<0.01, Student's t-test, two-sided).



Supplementary Figure 6. Luciferase reporter assays showed hydrogen peroxide (H_2O_2) and doxorubicin (Dox) could increase AKR1B10 promoter activity. Data shown are the mean ± s.d. of three independent experiments (*P<0.05, **P<0.01, Student's t-test, two-sided).