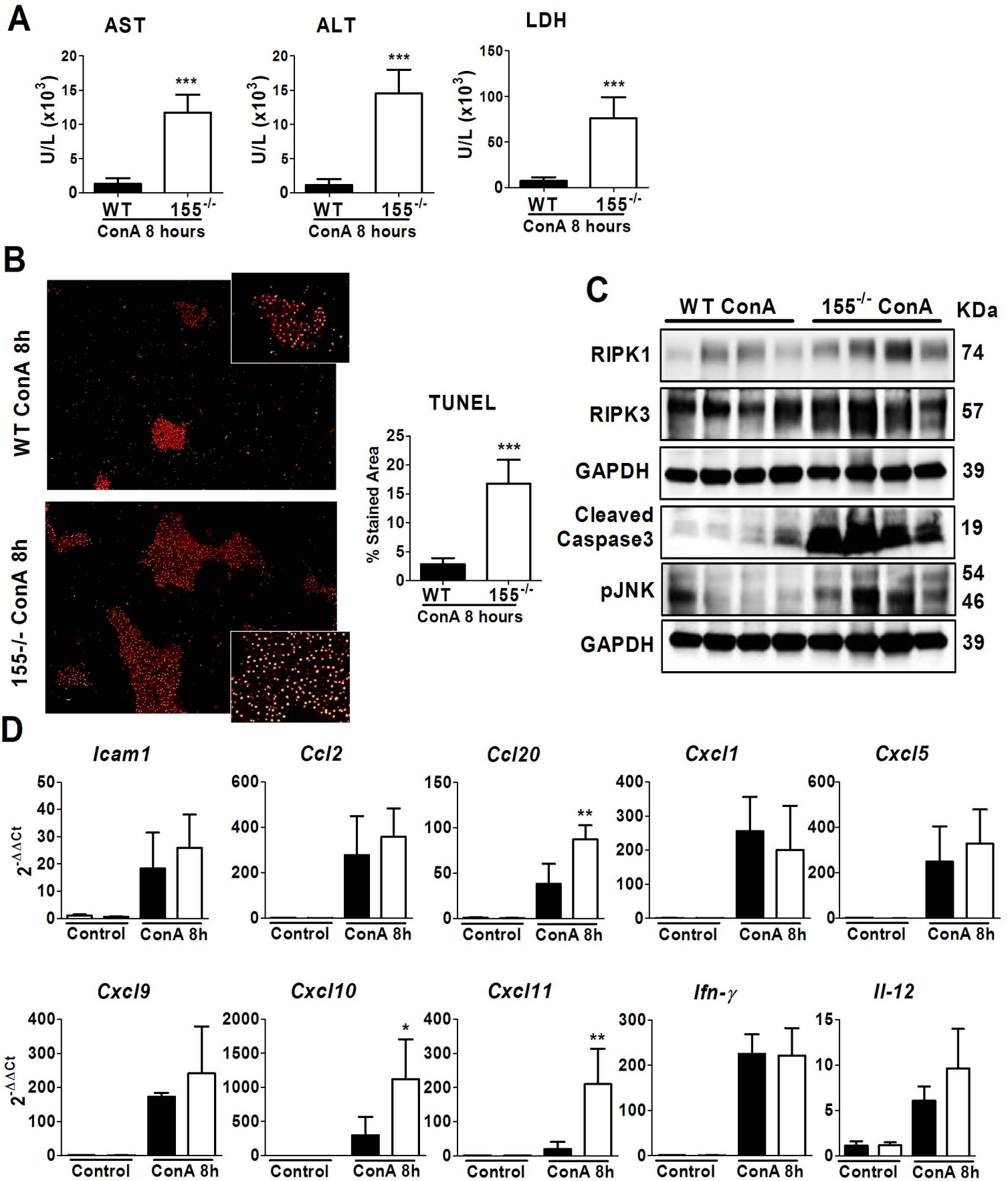
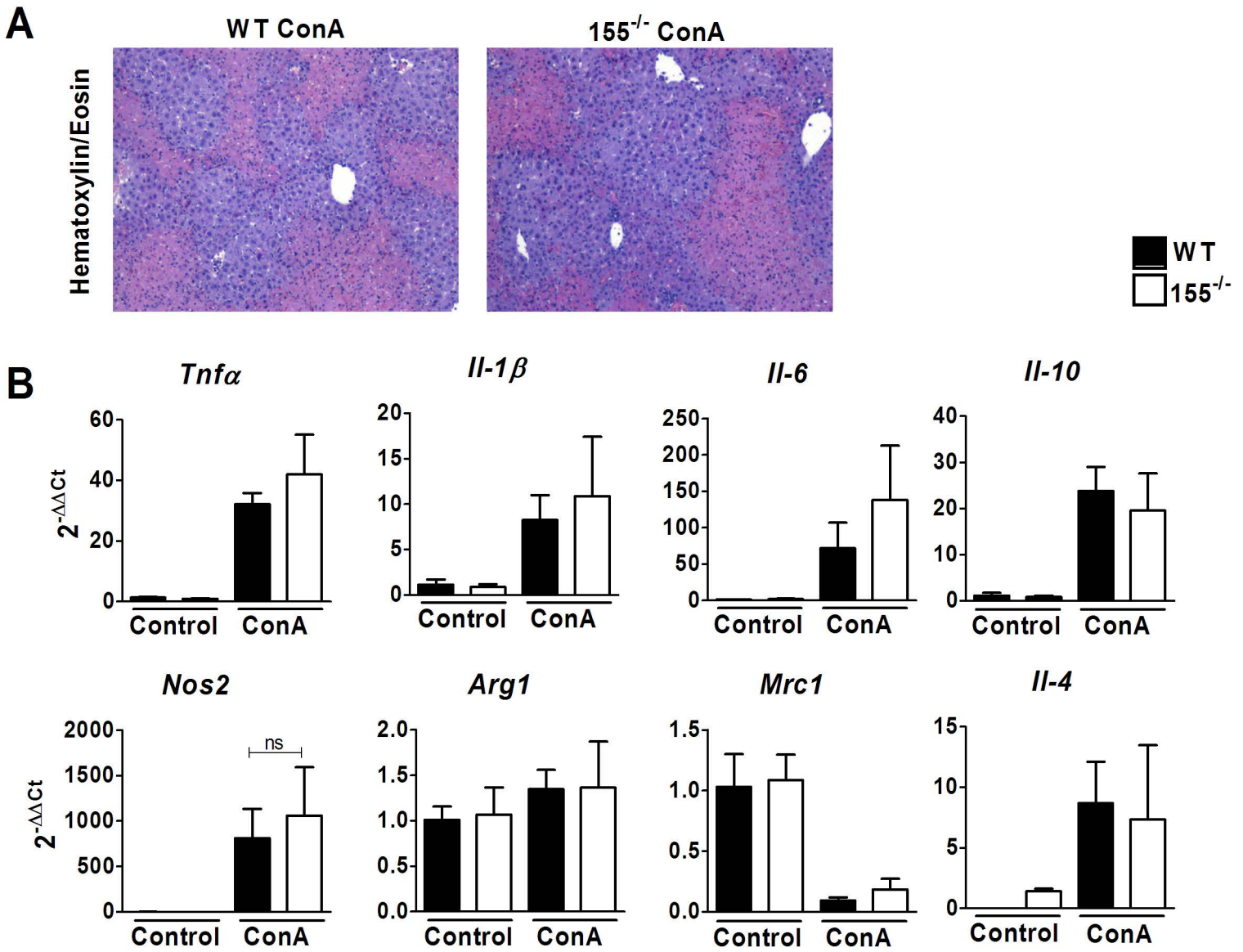


Supplementary Figure 1



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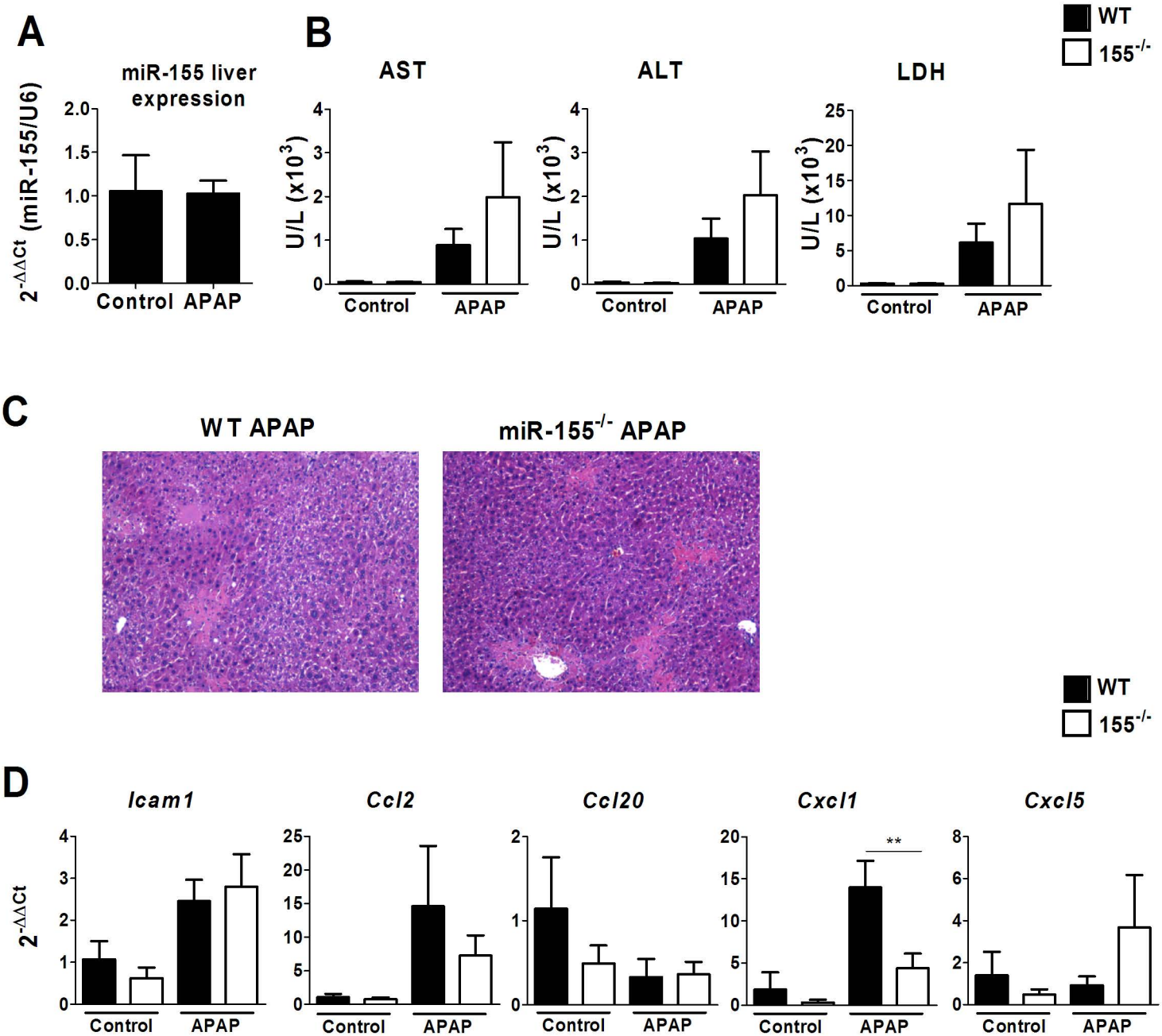

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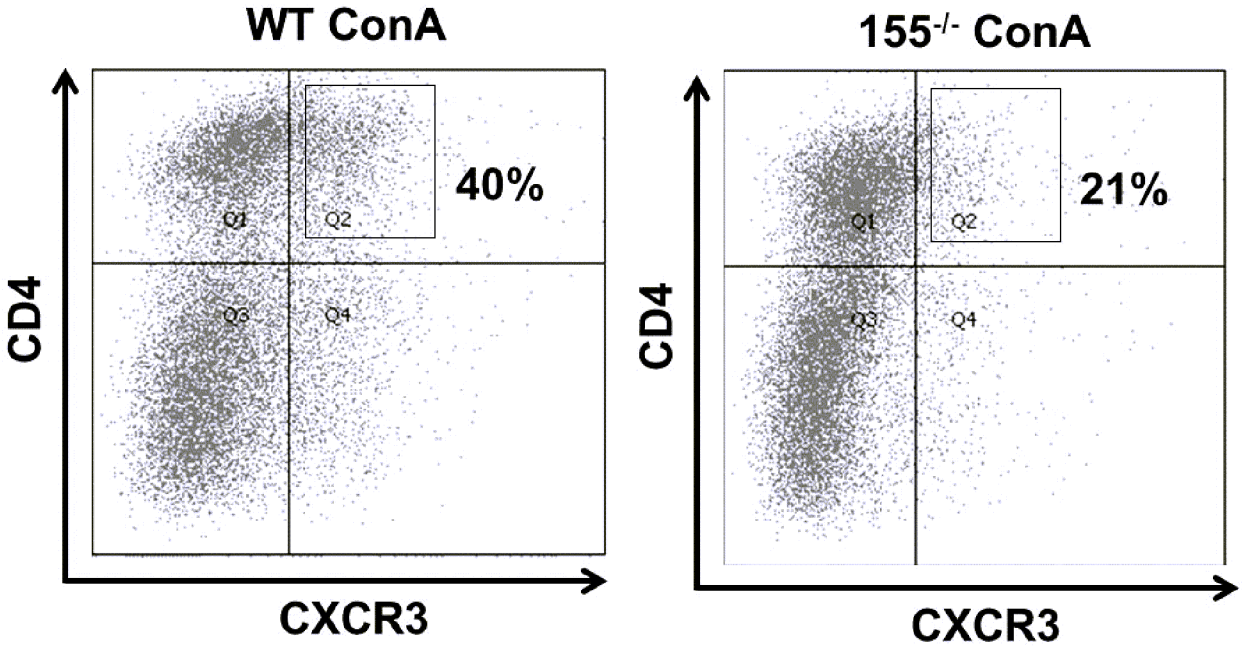
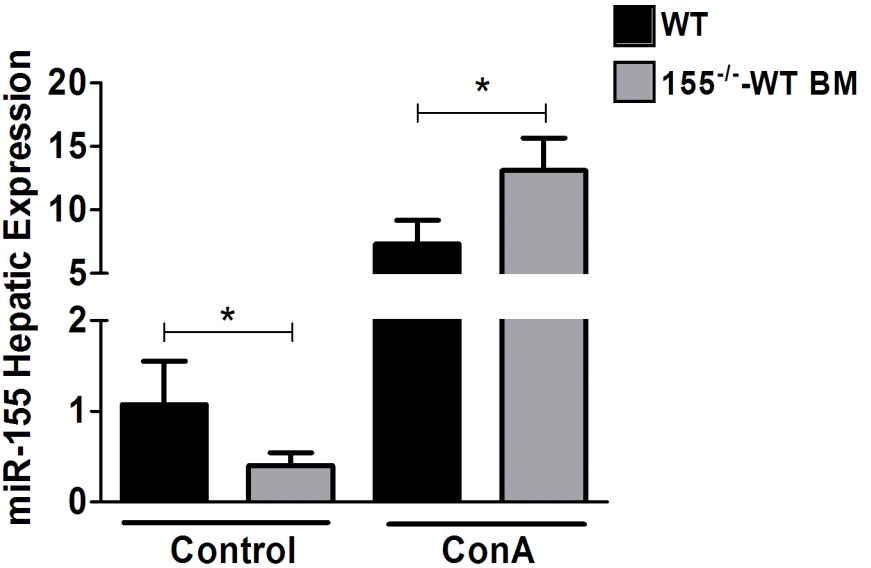


Supplementary Figure 4



Supplementary Figure 5

Supplementary figure 1. Wild type and miR-155$^{-/-}$ mice were treated with 10 mg/Kg ConA during 8 hours (WT, n=5; miR-155$^{-/-}$ n=6). **(A)** Liver transaminases and LDH levels were measured in serum. **(B)** Representative images of livers analysed by TUNEL assay staining at 40X magnification and quantification of the stained areas; ***p<0.001 with respect to WT ConA-treated animals. **(C)** Protein levels of RIPK1, RIPK3, cleaved Caspase 3 and pJNK were determined by Western Blot in livers of WT and miR-155$^{-/-}$ ConA-treated animals. GAPDH was used as a loading control. **(D)** Hepatic gene expression of several cytokines was measured by qPCR and expressed as $2^{-\Delta\Delta Ct}$ with respect to WT vehicle-treated mice. Significant p values are shown above the bars: *p< 0.05, **p<0.01, ***p<0.001 with respect to WT vehicle-treated animals.

Supplementary figure 2. Wild type and miR-155$^{-/-}$ mice were treated with physiological saline (WT, n=6; miR-155$^{-/-}$, n=6) or with 10 mg/Kg ConA (WT, n=5; miR-155$^{-/-}$ n=4) during 18 hours. **(A)** Representative haematoxylin/eosin staining of livers of WT and miR-155$^{-/-}$ ConA-treated animals (X100 magnifications). **(B)** Hepatic gene expressions of other inflammatory cytokines in by quantitative PCR and expressed as $2^{-\Delta\Delta Ct}$ with respect to WT vehicle-treated mice.

Supplementary figure 3. Deficiency in miR-155 slightly affects liver injury in an APAP model. Wild type and miR-155$^{-/-}$ animals were treated with physiological saline (WT, n=6; miR-155$^{-/-}$, n=5) or with 500 mg/Kg of acetaminophen (WT, n=4; miR-155$^{-/-}$, n=6) **(A)** Liver expression or miR-155 was measured in WT mice **(B)** Liver transaminases and LDH levels were measured in serum. **(C)** Representative haematoxylin/eosin staining of livers of WT or mir155$^{-/-}$ APAP-treated animals (X100 magnification) **(D)** Hepatic gene expression of several cytokines was measured by qPCR and expressed as $2^{-\Delta\Delta Ct}$ with respect to WT vehicle-treated mice. Significant p values are shown above the bars: **p< 0.01 with respect to WT vehicle-treated animals.

Supplementary figure 4. Representative flow cytometry plots from livers of ConA-treated mice showing $CD4^+CXCR3^+$ cells in WT and $155^{-/-}$ animals (40, 28 ± 7 ,8% and 21, 20 ± 0, 46% respectively, from total $CD4^+$ cells).

Supplementary figure 5. Hepatic expression of miR-155 in WT animals (n=3) and miR-$155^{-/-}$ WT-BM (n=5). Significant p values are shown above the bars: * $p < 0.05$ with respect WT vehicle- treated animals.

Supplementary Table 1. Demographic, clinical and laboratory characteristics of the AIH patients from whom liver biopsy was obtained (n=15)

Characteristics	AIH Patients
Age (years)	50±15
Male, n (%)	7 (47%)
Presence of ascites, n (%)	3 (20%)
AST (U/L)	414 ± 573
ALT (U/L)	487 ± 601
Serum bilirubin (mg/dL)	6. 5± 7.5
Serum albumin (g/L)	35 ± 6
INR	1.5 ±0.3
Platelet count (10^9/L)	145 ± 45
Leukocyte count (10^9/L)	6.2 ±1.8
C-reactive protein (mg/dL)	1.3 ±1.3
Fibrosis grade (% F1/F3/F4)	10/50/30
Alkaline Phosphatase (U/L)	242 ± 272
GGT (U/L)	221 ± 208

Quantitative variables expressed as mean ± standard deviation. Qualitative variables expressed as absolute number and frequency (%).

Supplementary Table 2 Demographic, clinical and laboratory characteristics of the AIH patients from whom PBMCs were obtained (n=15).

Characteristics	AIH Patients
Age (years)	58±17
Male, n (%)	5 (37.5%)
Presence of ascites, n (%)	2 (14.3%)
AST (U/L)	255±586
ALT (U/L)	309±772
Serum bilirubin (mg/dL)	2.7±4.9
Serum albumin (g/L)	39±5
INR	1.14±0.23
Platelet count (10^9/L)	220±97
Leukocyte count (10^9/L)	6.8±2.1
C-reactive protein (mg/dL)	0.27±0.26
Alkaline Phosphatase (U/L)	149±116
GGT (U/L)	182±236

Quantitative variables expressed as mean ± standard deviation. Qualitative variables expressed as absolute number and frequency (%).

Supplementary Table 3 Demographic, clinical and laboratory characteristics of patients with compensated (n=6) and decompensated cirrhosis (n=10).

Characteristics	Compensated cirrhosis	Decompensated cirrhosis
Age (years)	61±9	51±15
Male, n (%)	4(67%)	9 (90%)
Presence of ascites, n (%)	0	9 (90%)
AST (U/L)	32±8	218 ± 296
ALT (U/L)	28±90	109 ± 121
Serum bilirubin (mg/dL)	117±47	10.4 ± 11
Serum albumin (g/L)	86±58	27 ± 6
INR	0,7±0,2	1.9 ±0.3
Platelet count (10^9/L)	139±73	111 ± 93
Leukocyte count (10^9/L)	6,4±1,7	8.9 ± 5.3
C-reactive protein (mg/dL)	0,9±1,6	4.7 ±4
Child-Pugh score	5±0	10 ± 2
Alkaline Phosphatase (U/L)	117±47	137 ± 85
GGT (U/L)	86±58	258 ± 445

Quantitative variables expressed as mean ± standard deviation. Qualitative variables expressed as absolute number and frequency (%).

SUPPLEMENTARY MATERIAL

Isolation of mononuclear liver cells and flow cytometry analysis

Livers were collected from the mice and physically disaggregated through a 70 μm cell strainer. Next, non-parenchymal cells were separated by density gradient with Ficoll (GE Healthcare, IL, US); afterwards the mononuclear cell layer was collected. Cells were stained with fluorescents antibodies as follows: macrophages were stained with Rat Anti-Mouse F4/80-PE (e-Bioscience) and Rat Anti-Mouse CD11b-Alexa Fluor 647 (BD Bioscience) to discriminate infiltrating monocytes and resident liver macrophages; T cells were stained with Rat Anti-Mouse CD4-PE-Cy™7, Rat Anti-Mouse CD8a-FITC and Hamster Anti-Mouse CD183-Brilliant Violet 421 (CXCR3); NKT cells were stained with Rat Anti-Mouse CD3-Alexa Flour 647 and Mouse Anti-Mouse NK-1.1-FITC. Otherwise, to detected Tregs, spleen and livers were disaggregated and mononuclear cells were obtained as described above. Next, mononuclear cells were treated with the Mouse Foxp3 Buffer Set (BD) following the manufacturer's instructions and stained with Rat anti-Mouse Foxp3-Alexa Fluor 488 (BD) and Rat Anti-Mouse CD4-PE-Cy™7. The samples were evaluated by flow cytometry (FACS Canto II; BD) and the data were analysed using BD FACSDIVA™ Software (BD).

Fluorescent-conjugated antibodies

Antibody	Fluorochrome	Catalog #	Brand
Rat Anti-Mouse CD4	PE-Cy™7	552775	BD Bioscience
Rat Anti-Mouse CD8a	FITC	553030	BD Bioscience
Hamster Anti-Mouse CD183	Brilliant Violet 421	562937	BD Bioscience
Rat Anti-Mouse CD3	Alexa Flour 647	557869	BD Bioscience
Mouse Anti-Mouse NK-1.1	FITC	553164	BD Bioscience
Rat Anti-Mouse F4/80	PE	12-4801-80	e-Bioscience
Rat Anti-Mouse CD11b	Alexa Fluor 647	557686	BD Bioscience

Rat anti-Mouse Foxp3	Alexa Fluor 488	560407	BD Bioscience

Cytokine detection on cell culture supernatant

Interleukin (IL) IL-2, IL-4, IL-5, IL-10, interferon gamma (IFNγ) and tumour necrosis factor alpha (TNFα) concentrations were determined in the supernatants of cultured $CD4^+$ cells using a Milliplex® MAP Mouse Cytokine/Chemokine Detection Panel (a multiple immunoassay based on Luminex Technology) following the manufacturer's instructions (EMD Millipore, Germany).

Chimerism analysis

100 µl of peripheral blood was collected from the tail; total blood was stained with anti-CD45.1 and anti-CD45.2 antibodies (BD Bioscience). Next, erythrocytes were lysed with Lysing Buffer following the manufacturer's instructions (BD PhamLyse). Relative percentages of $CD45.1^+$ cells (of donor origin) with respect to total $CD45^+$ were calculated by flow cytometry analysis in all the transplanted mice.

Determination of caspases activity

To further elucidate liver damage, we performed an assay to detect Caspase 3 and 7 activity. First, the liver tissue was homogenized in an hypotonic buffer (HEPES 25 mM pH7, 5, $MgCl_2.6H_2O$ 5 mM, EGTA 1mM and 1 µg/ml of protease inhibitors). Afterwards protein concentrations were determined by colorimetric assay with Bradford (Bio-Rad, CA, US). Next, 100 µg/ml of whole liver protein was mixed with Caspase-GLO 3/7 Assay (Promega, WI, USA) following the manufacturer's instructions. After 120 minutes of incubation, luminescence was detected and quantified in a Luminometer (FLUOStar Optima; BMG LabTech, Germany).

Immunohistochemistry

Paraffin-embedded liver sections were stained with CD45 (1:40, BD Pharmigen) or MPO (1:200, Abcam, Cambridge, UK) antibodies overnight at 4°C. Afterwards, the sections were incubated with secondary antibodies (Dako, Glostrup, Denmark) for 30 minutes at room temperature, then stained with 3,3'-diaminobenzidine (DAB, Dako) and counterstained with haematoxylin. The sections were visualized at a magnification of 200 and positive areas were quantified in 15 different fields. The results were expressed as the percentage of positive-stained area.

TUNEL Assay

Paraffin-embedded liver sections were stained with the In Situ Cell Death Detection Kit, TMR red (Sigma-Aldrich) following the manufacturer's instructions. To counterstain the nuclei the Vectashield Antifade Mounting Medium with DAPI (Vector Laboratories) was used. Sections were visualized at a magnification of 40x and apoptotic areas were quantified in 15 different fields. Percentage of stained area was calculated with the image software Image J.

Immunoblot and protein analysis

Protein extracts were electrophoresed and then blotted following standard procedures. The blots were incubated with primary antibodies for cleaved Caspase 3 (Cell Signaling Technology, Barcelona, Spain), phospho-JNK (Cell Signaling Technology), RIPK1 (BD Transduction Laboratories) and RIPK3 (ProSci, CA, US). Anti-rabbit-HRP (Bio-Rad) and anti-mouse-HRP (Bio-Rad) were used as secondary antibodies. GAPDH (Bio-Rad) was used as the loading control.

Extraction of RNA, quantification of miRNA and gene expression

Whole RNA containing mRNA and miRNA was extracted using Trizol following the manufacturer's instructions (Life Technologies, Carlsbad, CA). MiRNA quantification

was performed using the Mir-X miRNA First-Strand Synthesis Kit according to the manufacturer's instructions (Takara Bio Europe/Clontech, Saint-Germain-en-Laye, France). Data were normalized using U6 snoRNA as the endogenous control. The human or mice sequences of miR-155 were obtained from the miRbase database: hsa-miR-155 TTAATGCTAATCGTGATAGGGGT and mmu-miR-155 TTAATGCTAATTGTGATAGGGGT. Custom primers were used (Integrated DNA Technologies, BVBA, Leuven, Belgium). mRNA quantification was accomplished using the Taqman gene expression assay probe and primers. Both miRNA and mRNA levels were measured by real-time quantitative PCR (qPCR) with an ABI 7900 HT cycler (Thermo Fisher, MA, US). Expression values were calculated based on the $\Delta\Delta$Ct method and expressed as $2^{-\Delta\Delta Ct}$.