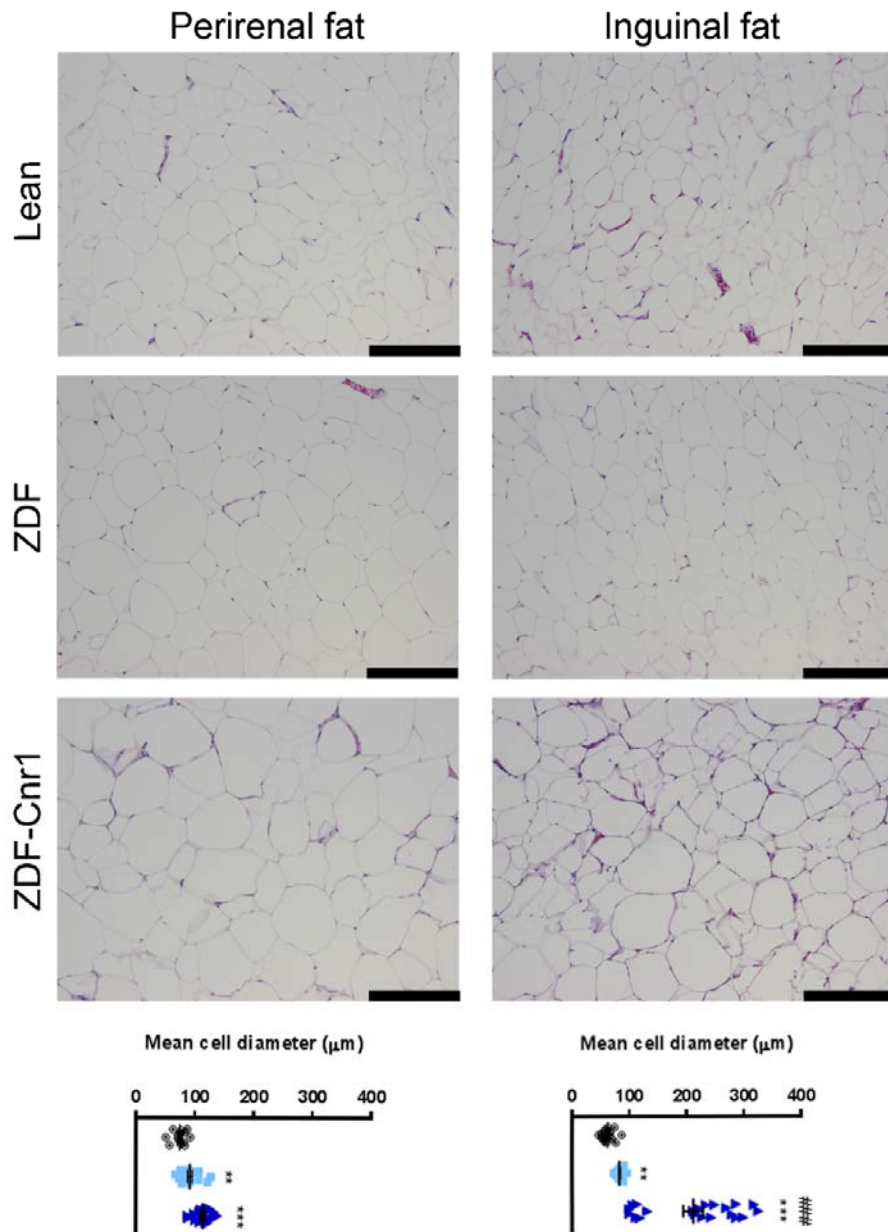


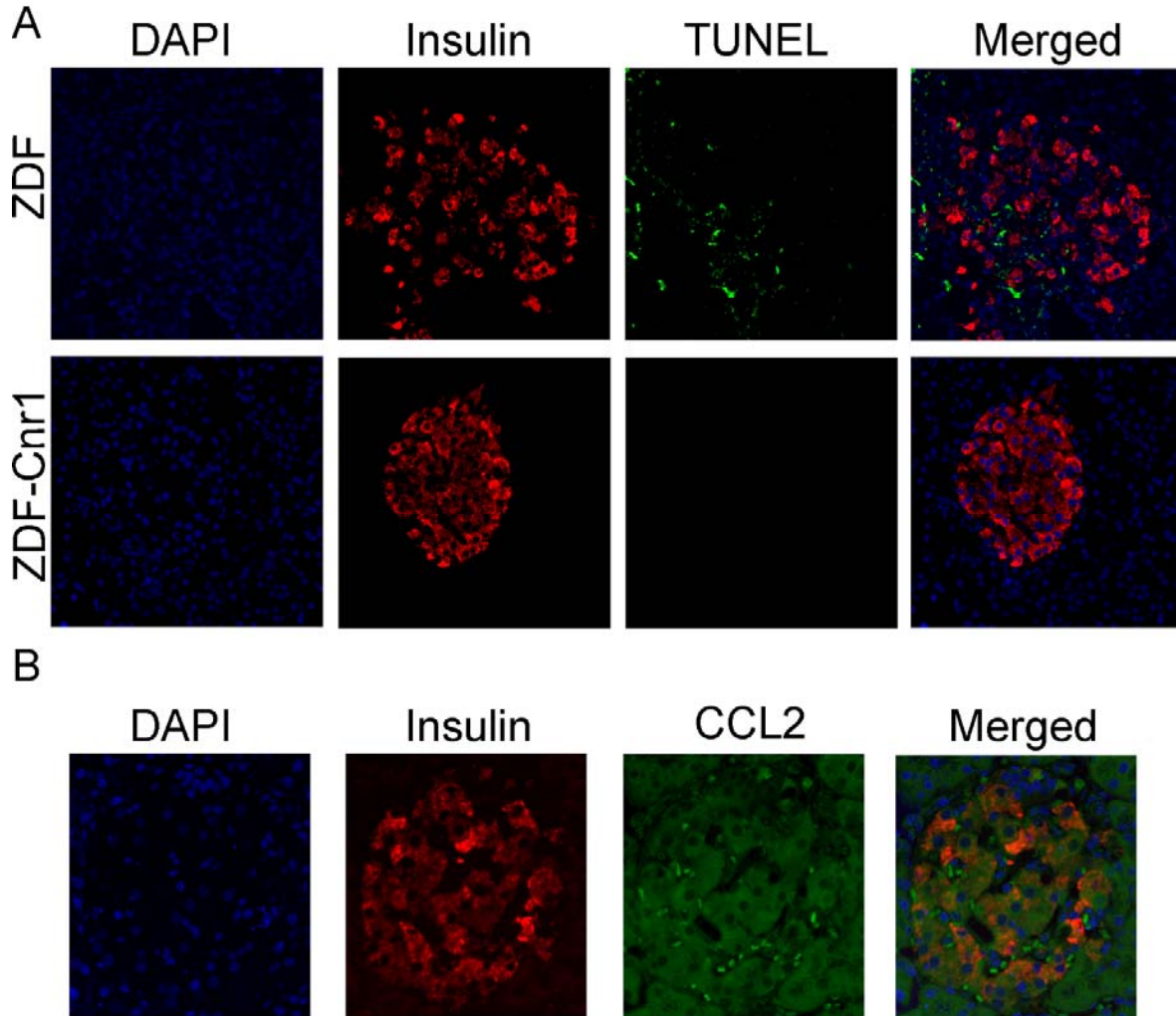
SUPPLEMENTARY DATA

**Supplementary Figure S1. Genetic deletion of Cnr1 leads to an increase in adipocyte size in inguinal fat.** Related to Figure 1. Representative H&E stain images (n = 6-7 images per mouse) of perirenal (as visceral fat) and inguinal (\*subcutaneous) adipose tissue and quantification of adipocyte diameter in both tissue from Lean (open circles), ZDF (light blue) and ZDF-Cnr1 (dark blue) at 26 week-old. Scale bars, 200  $\mu$ m. Data represent mean  $\pm$  SEM (n = 3 rats per group). Significant difference from corresponding value in lean (\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001) or ZDF rats (##P < 0.01, ###P < 0.001).



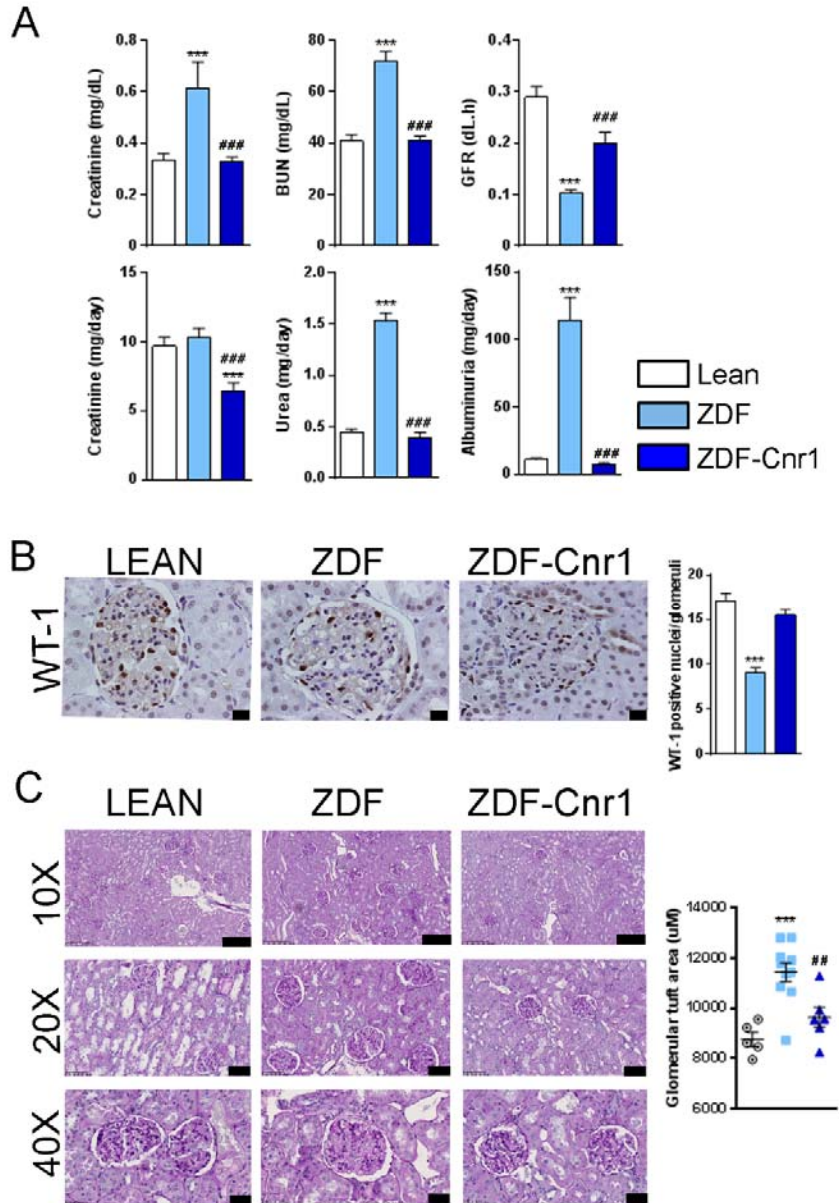
SUPPLEMENTARY DATA

**Supplementary Figure S2. Genetic deletion of Cnr1 protects against  $\beta$ -cell death.** Related to Figure 3. (A) Representative TUNEL stain image of pancreatic islets from ZDF and ZDF-Cnr1 rats. (B) Double immunostaining for insulin and CCL2 in pancreatic islets.



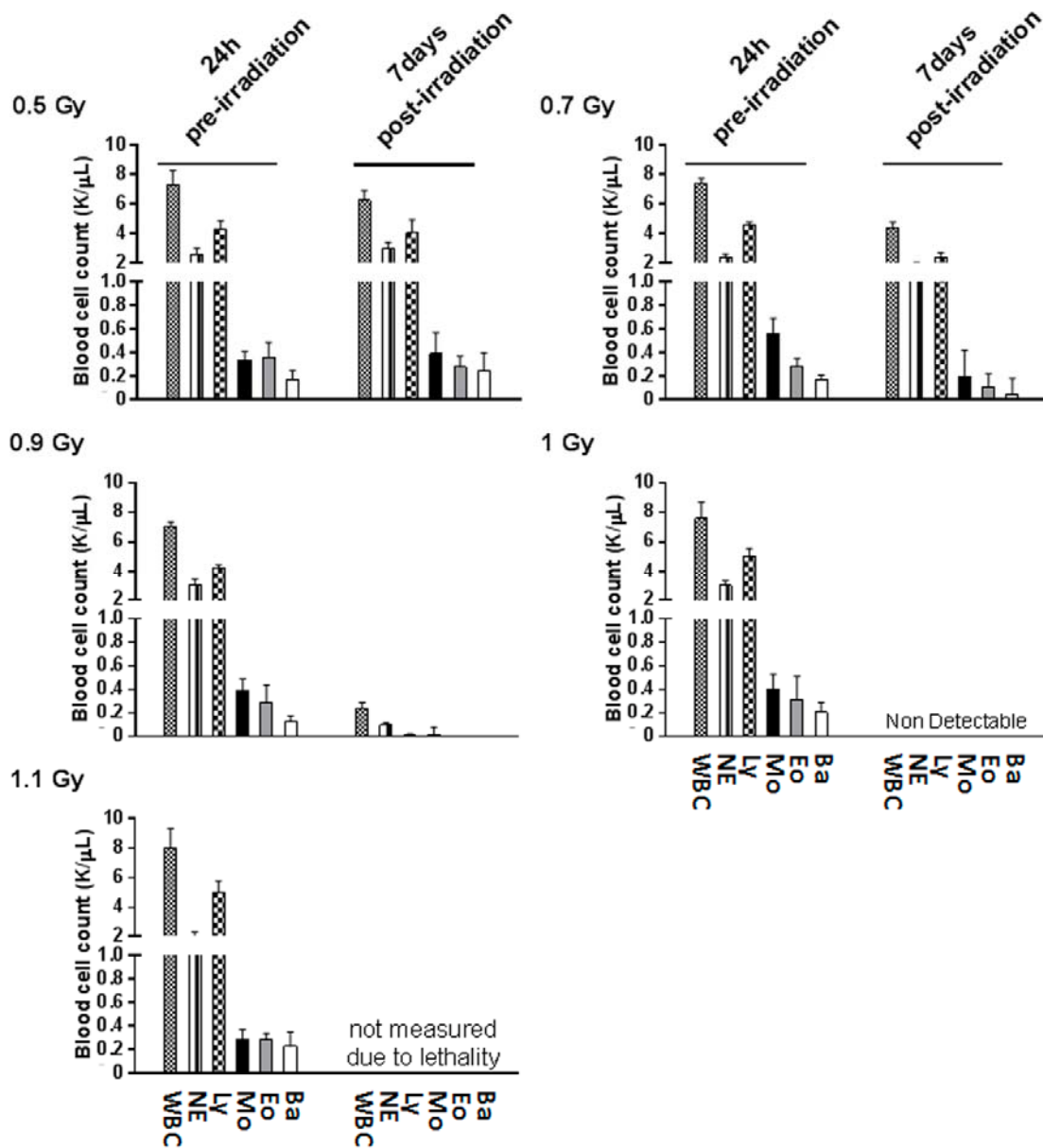
SUPPLEMENTARY DATA

**Supplementary Figure S3. Genetic deletion of Cnr1 protects against the development of diabetic nephropathy.** (A) Serum concentration of creatinine and blood urea nitrogen (BUN); Urinary clearance of creatinine, BUN and albumin; Glomerular filtration rate in lean, ZDF and ZDF-Cnr1 rat. (B) Podocytes identified in glomeruli of lean, ZDF and ZDF-Cnr1 rats by WT-1 immuno-staining. (C) PAS staining and glomerular enlargement quantification. Columns and bars represent mean  $\pm$  SEM (n = 10 rats per group). Significant difference from corresponding value in lean (white bars) (\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001) or ZDF rats (light blue bars) (##P < 0.01, ###P < 0.001).



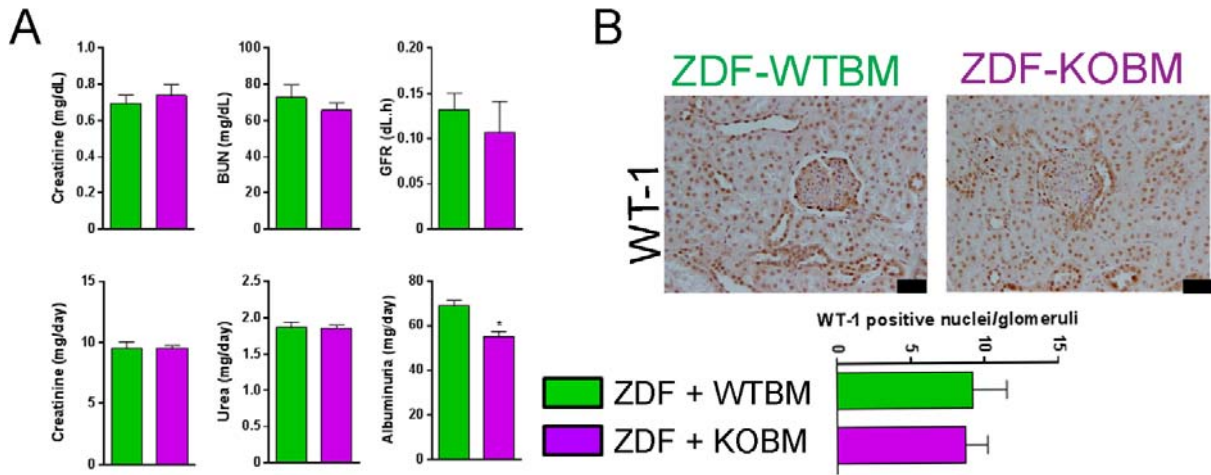
SUPPLEMENTARY DATA

**Supplementary Figure S4. Determination of the optimal radiation dose required to eliminate total white blood cells without being lethal.** Related to Figure 4. Total body radiation exposure from a <sup>137</sup>Cs source was varied between 0.5 to 1.1 Gy and total blood cell count was performed 24h before irradiation and 7 days post-irradiation. WBC: White Blood Cells, NE: Neutrophils, Ly: Lymphocytes, Mo: Monocytes, Eo: Eosinophils and Ba: Basophils. Columns and bars represent mean ± SEM (n = 3 rats per group).



SUPPLEMENTARY DATA

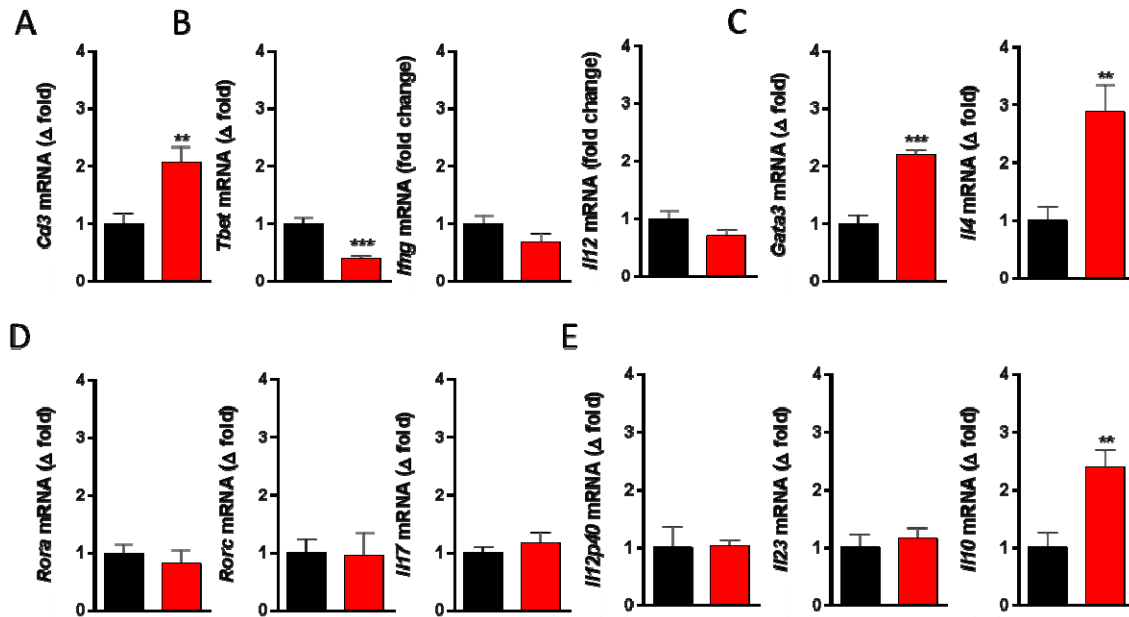
**Supplementary Figure S5. Transplantation with *Cnr1* deficient bone marrow does not prevent the development of diabetic nephropathy.** Related to Figure 4. (A) Serum concentration of creatinine and blood urea nitrogen (BUN); Urinary clearance of creatinine, BUN and albumin; Glomerular filtration rate in ZDF rats receiving wild-type BM (green columns) or *Cnr1*<sup>-/-</sup> BM (purple columns). (B) Podocytes identified in glomeruli of wild-type BM (green columns) and *Cnr1*<sup>-/-</sup> BM (purple columns) by WT-1 immuno-staining. Columns and bars represent mean ± SEM (n = 5 rats per group). Significant difference from corresponding value in ZDF rats receiving wild-type BM (\**P* < 0.05).





SUPPLEMENTARY DATA

**Supplementary Figure S6. GeRP-Mediated Knockdown of *Irf5* in ZDF Rats macrophages leads to a blunted lymphocyte response in pancreatic islets.** Related to Figure 7. (A) *Cd3* gene expression as marker of T lymphocyte infiltration. (B) Gene expression of *Tbet*, *Ifng* and *Il12* as Th1 response markers. (C) Gene expression of *Gata3* and *Il4* as Th2 response markers. (D) Gene expression of *Rora*, *Rorc* and *Il17* as Th17 response markers. (E) Gene expression for *Il12p40*, *Il23* and *Il10* in pancreatic islets. Columns and bars are means±SEM from 6 rats/group. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.005$  relative to control siRNA-treated group



SUPPLEMENTARY DATA

**Supplementary Table S1. Serum parameters in whole body irradiated-BMT rats.**

<b>Parameters</b>	<b>ZDF-WT BM cells (n=5)</b>	<b>ZDF-KO BM cells (n=5)</b>
<b>Triglycerides (mg/dL)</b>	108.1 ±10.1	105.8 ±4.1
<b>Free fatty acids (µM)</b>	176.8 ±6.3	182.1 ±12.5
<b>Total cholesterol (mg/dL)</b>	94.7 ±3.3	98.1 ±2.9
<b>Adiponectin (ng/mL)</b>	486.3 ±32.5	472 ± 43.7
<b>Leptin (pg/mL)</b>	3,204.8 ±219.6	3,078.7 ±97.9

Columns and bars represent mean±SEM. Significant difference from corresponding value in ZDF rats receiving WT BM cells(P>0.05\*, P>0.01\*\*, P<0.001\*\*\*).

SUPPLEMENTARY DATA

**Supplementary Table S2. PCR parameters for *Cnr1* and *Lepr* amplification.**

<i>Cnr1</i>		
Cycle Step	Temp (°C)	Time
1	94	3 min
2	94	30 sec
3	56	30 sec
4	68	30 sec
5	72	5 min

**\* 45 cycles**

<i>Lepr</i>		
Cycle Step	Temp (°C)	Time
1	95	5 min
2	95	30 sec
3	58	30 sec
4	68	30 sec
5	68	5 min

**\* 35 cycles**

*Cnr1* smF: 5'-gatgcaggccttctaccac, smR: 5'-gctgtctttacgggtggaata.

*Fa* smF: 5'-cgtatggaagtcacagatgatgtatt, *Fa*-smR: 5'-cctctcttacgattgtagaattctct.

After *Fa* PCR, 20 µl of PCR reaction were digested in a total volume of 30 µL with *MspI* (FastDigest *MspI*, Thermo scientific, #FD0544) in order to digest the mutant allele to ~79 bp and 39 bp. *Cnr1* and *Fa* PCR products were resolved on 4% agarose gel and revealed by GreenGlo™ Safe DNA Dye (Denville Scientific inc, CA3600, Metuchen, NJ) using a Gel scanner G:BOX (SYNGENE, Frederick, MD).



SUPPLEMENTARY DATA

**Supplementary Table S3. list of antibodies used for immuno-histology.**

<b>Proteins</b>	<b>Reference</b>	<b>Supplier</b>	<b>Dilution</b>
CB1R	L15	Gift from Dr Ken Mackie (Uni of Indiana, USA)	1/250
Insulin	Ab7842	Abcam, USA	1/100
CD68	Ab31630	Abcam, USA	1/200
CCL2	Ab25124	Abcam, USA	1/800
WT-1	05-753	Millipore (USA)	1/200
IRF5	Ab181553	Abcam, USA	1/200

SUPPLEMENTARY DATA

**Supplementary Table S4. list and sequence of siRNAs used.**

<b>RAT</b>	
<b><i>Cnr1</i></b> 5'-GCAUCAAGAGCACCGUAAAUU-3'	<b>Control</b> 5'-GCAUCAAGUCUACCGUAAAUU-3'
<b><i>Irf5:</i></b> 5'-GGUUACAGAUGGUGGCUGAUU-3'	<b>Control:</b> 5'-GGUUACAGUACGUGGCUGAUU-3'
<b>HUMAN</b>	
<b><i>CNRI:</i></b> 5'-CCGCAAAGAUAGCCGCAACUU-3'	<b>Control:</b> 5'-CCGCAAAGUAUGCCGCAACUU-3'
<b><i>MAPK14:</i></b> 5'-GGCACACAGAUGAUGAAAUUU-3'	<b>Control:</b> 5'-GGCACACACUAGAUGAAAUUU-3'
<b><i>MAPK11:</i></b> 5'-GCACGUUCAAUUCCUGGUUUU-3'	<b>Control:</b> 5'-GCACGUUCUUAUCCUGGUUUU-3'

SUPPLEMENTARY DATA

**Supplementary Table S5. list of antibodies used for western-blotting.**

<b>Proteins</b>	<b>Reference</b>	<b>Supplier</b>	<b>Dilution</b>
CB1R	N/A	Immunogenes, Hungary	1/750
$\alpha$ -p38MAPK	#4511	Cell Signalling Technology (USA)	1/1000
$\alpha$ -p38MAPK	#9215	Cell Signalling Technology (USA)	1/1000
$\alpha$ -pERK1/2	#4377	Cell Signalling Technology (USA)	1/1000
$\alpha$ -pSAPK/JNK	(#9251	Cell Signalling Technology (USA)	1/1000
$\alpha$ -pSAPK/JNK	#4668	Cell Signalling Technology (USA)	1/1000
$\alpha$ -phospho-c-jun	(#9261	Cell Signalling Technology (USA)	1/1000
$\alpha$ -pSTAT3	#9145	Cell Signalling Technology (USA)	1/1000
$\alpha$ -total-ERK1/2	(#4695	Cell Signalling Technology (USA)	1/1000
$\alpha$ -total-SAPK/JNK	(#9252	Cell Signalling Technology (USA)	1/1000
$\alpha$ -total-STAT3	(#4904	Cell Signalling Technology (USA)	1/1000
p38MAPK $\alpha$	Sc-535	Santa Cruz USA	1/1000
$\beta$ -actin	Ab49900	Abcam, USA	1/1000