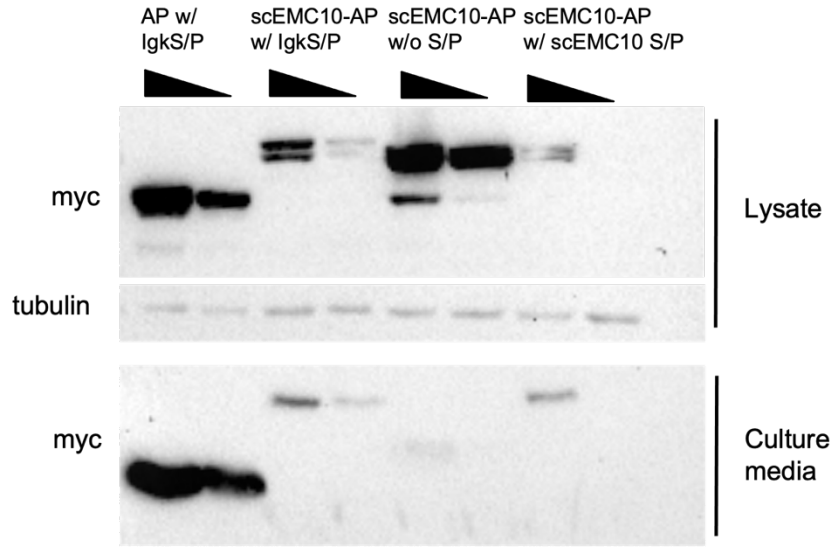
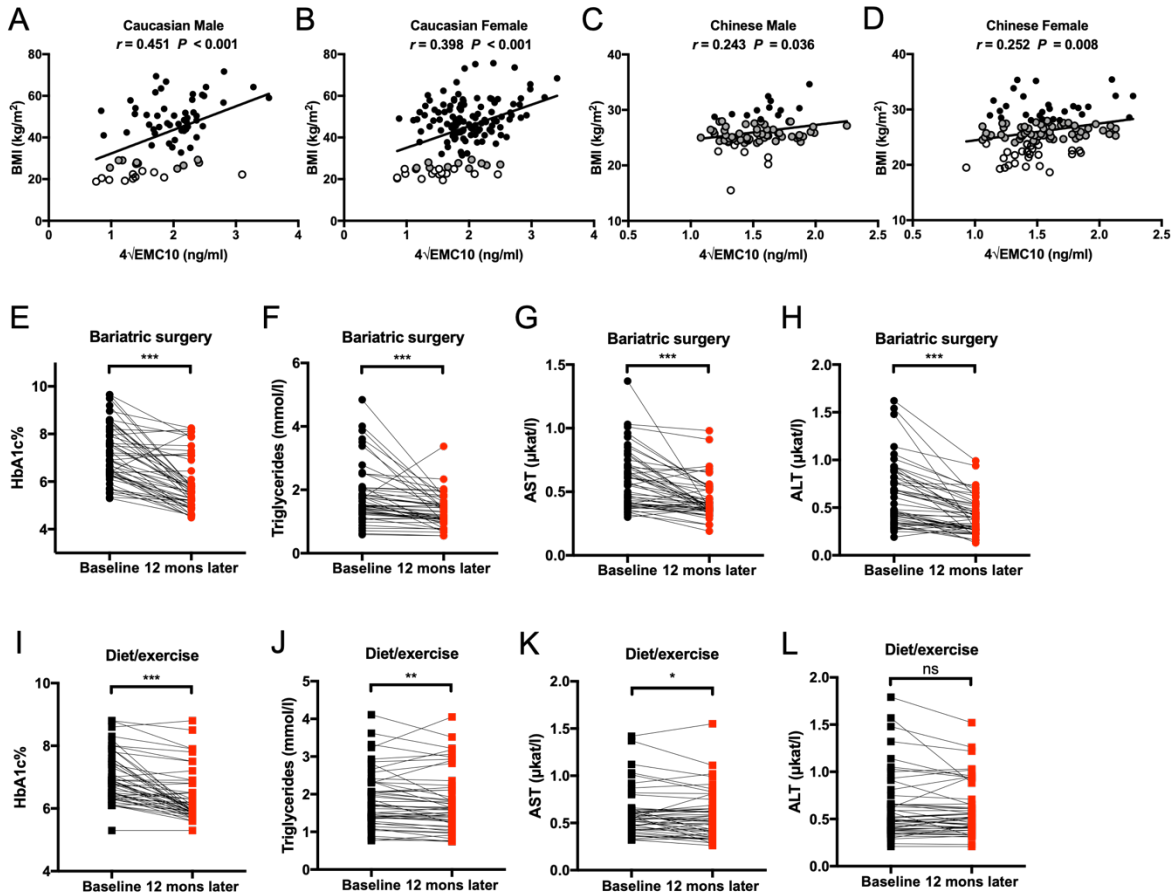
Supplementary Figure 1



Supplementary Figure 1. In vitro confirmation of scEMC10 as a secreted protein

Western blotting for cell lysate or culture media from 293T cells 48h after transfection with myc-tagged alkaline phosphatase or scEMC10-AP with or without Igk signal peptide or scEMC10 endogenous signal peptide plasmid constructs. AP, alkaline phosphatase; S/P, signal peptide; w/, with; w/o, without.

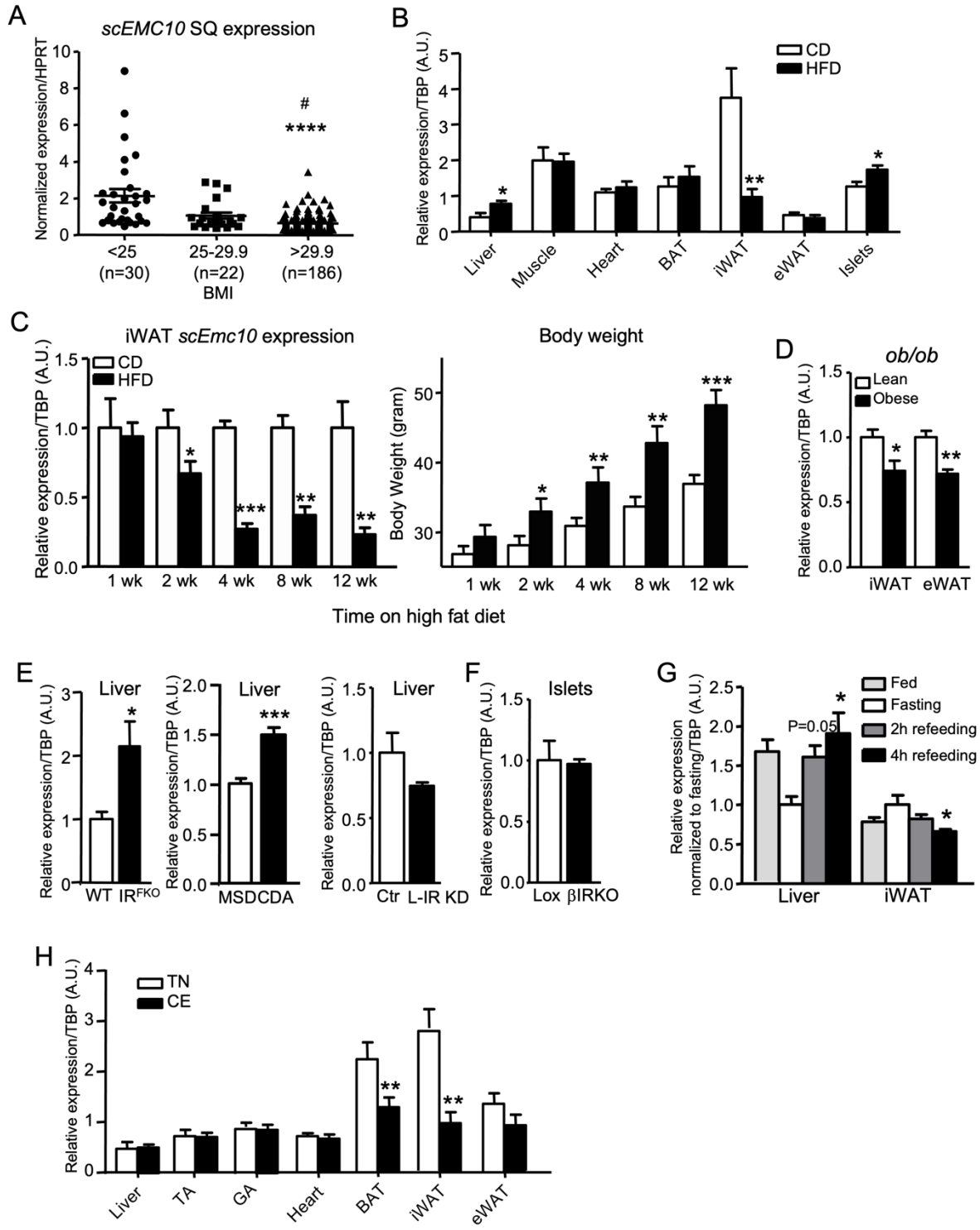
Supplementary Figure 2



Supplementary Figure 2. Association of serum EMC10 levels with BMI in humans and changes of metabolic parameters before and after weight loss in obese patients

(A-D) Associations of serum EMC10 levels with BMI in male or female Caucasian or Chinese Han cohort including lean, overweight and obese subjects. Changes of HbA1c, serum triglycerides, AST, and ALT before and 12 months after bariatric surgery **(E-H)** or diet/exercise **(I-L)** in subjects of a Caucasian weight-loss cohort.

Supplementary Figure 3



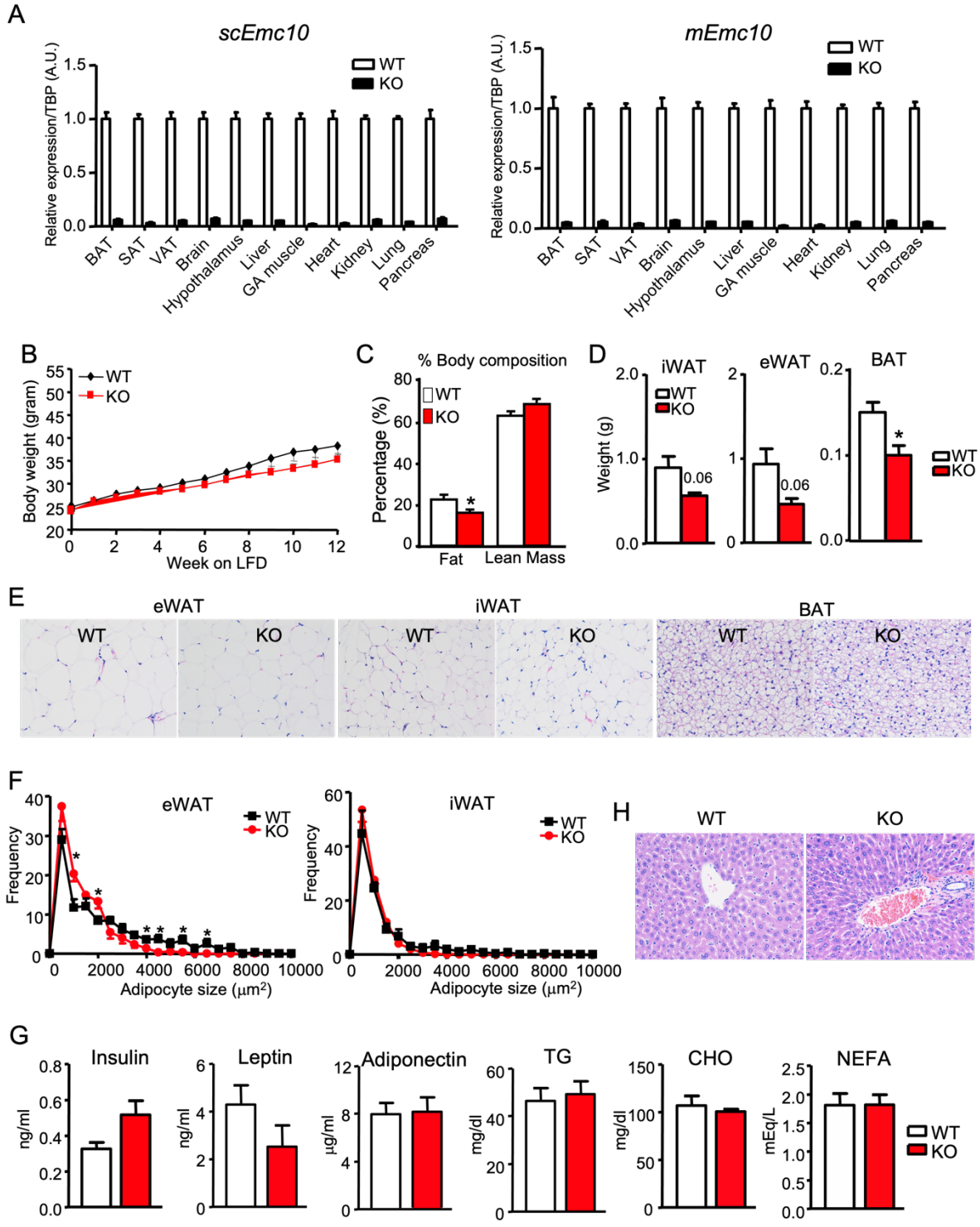
Supplementary Figure 3. Regulation of *scEMC10* gene expression in humans and mouse models

(A) Human *scEMC10* mRNA in subcutaneous (SQ) fat from lean, overweight and obese patients. (n number indicated). All data are presented as mean +/- SEM. ****, p<0.0001 (vs <25); #, p<0.05 (vs 25-29.9).

(B) *scEmc10* mRNA in liver, muscle, heart, brown adipose tissue (BAT), subcutaneous (inguinal, iWAT), visceral (epididymal, eWAT) white adipose tissue and pancreatic islets from chow diet (CD) or high fat diet (HFD) fed C57BL/6 mice (n=6 per group). **(C)** iWAT (inguinal white adipose tissue) *scEmc10* mRNA levels

and body weights of C57BL/6 mice on HFD (n=5-6 per group). **(D)** *scEmc10* mRNA in subcutaneous (inguinal, iWAT), and visceral (epididymal, eWAT) white adipose tissue from lean and obese ob/ob mice (n=6 per group). **(E)** *scEmc10* mRNA in liver from WT and IR^{FKO} (adipose tissue-specific insulin receptor KO) mice, or C57BL/6 mice fed with control (MSD) or choline-deficient and methionine-restricted (0.1%), high-fat diet (60% Kcal from fat) (CDA), or IR^{flox} mice 7-days after injection with AAV-GFP (Ctr) or AAV-Cre (acute liver insulin receptor knockdown model, L-IR KD) (n=5-7 per group). **(F)** *scEmc10* mRNA in pancreatic islets from control (Lox) and beta-cell specific insulin receptor KO (βIRKO) mice (n=3). **(G)** *scEmc10* mRNA in liver or subcutaneous (inguinal, iWAT) white adipose tissue from C57BL/6 mice in the fed, 24h fasting, 2h or 4h refeeding states (n=5-7 per group). **(H)** *scEmc10* mRNA in liver, tibialis anterior (TA) and gastrocnemius (GA) muscle, heart, brown adipose tissue (BAT), subcutaneous (inguinal, iWAT) and visceral (epididymal, eWAT) white adipose tissue from thermoneutral (TN) or cold exposure (CE) treated C57BL/6 mice (n=6 per group). All data are presented as mean +/- SEM. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

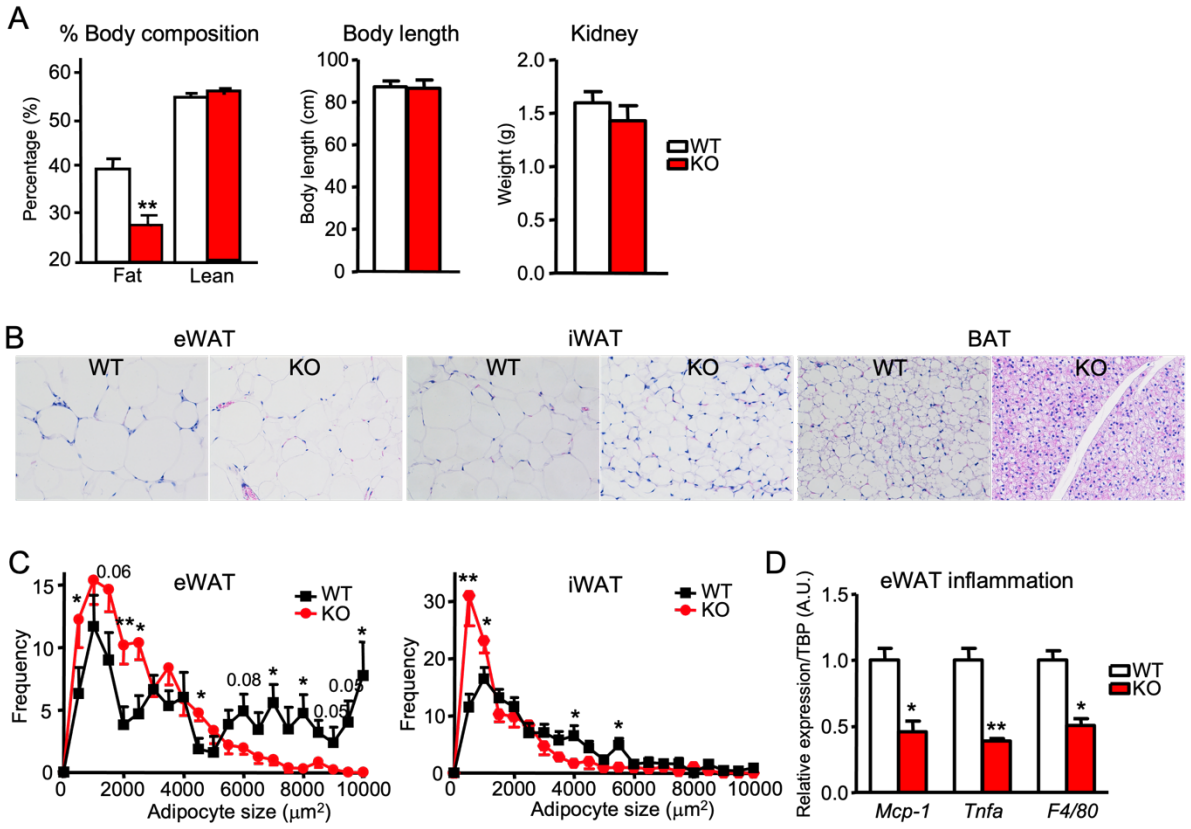
Supplementary Figure 4



Supplementary Figure 4. Phenotypes of *Emc10* knockout mice fed with low fat diet (LFD)
(A) *scEmc10* and *mEmc10* mRNA in brown (BAT), subcutaneous (SAT) and visceral (VAT) adipose tissue, brain, hypothalamus, liver, gastrocnemius (GA) muscle, heart, kidney, lung and pancreas tissue dissected from male WT (open) or KO (black) CD-fed mice (n=6-7 per group). **(B)** Body weights of male (WT, black diamond), and KO (red square) on C57BL/6 background on LFD (n=6-7 per group). Percentage of body composition **(C)**, and weights of subcutaneous (inguinal, iWAT), visceral (epididymal, eWAT) and brown

(BAT) adipose tissues **(D)** from male WT (open), and KO (red) mice fed with 12-wks of LFD (n=6-8 per group). **(E)** Representative images of hematoxylin and eosin (H&E)-stained sections of eWAT, iWAT, and BAT from male WT and KO mice fed LFD. **(F)** Quantification of eWAT and iWAT adipocyte size from male WT (black square) and KO (red circle) mice fed LFD. **(G)** Plasma insulin, leptin, adiponectin, triglyceride (TG), cholesterol (CHO), and non-esterified fatty acid (NEFA) in male WT (open), and KO (red) mice fed with 12-wks of LFD in the fed state (n=6-7 per group). **(H)** Representative images of H&E-stained sections of livers from male WT and KO mice fed with 12-wks of LFD. All data are presented as mean +/- SEM. *, $p<0.05$.

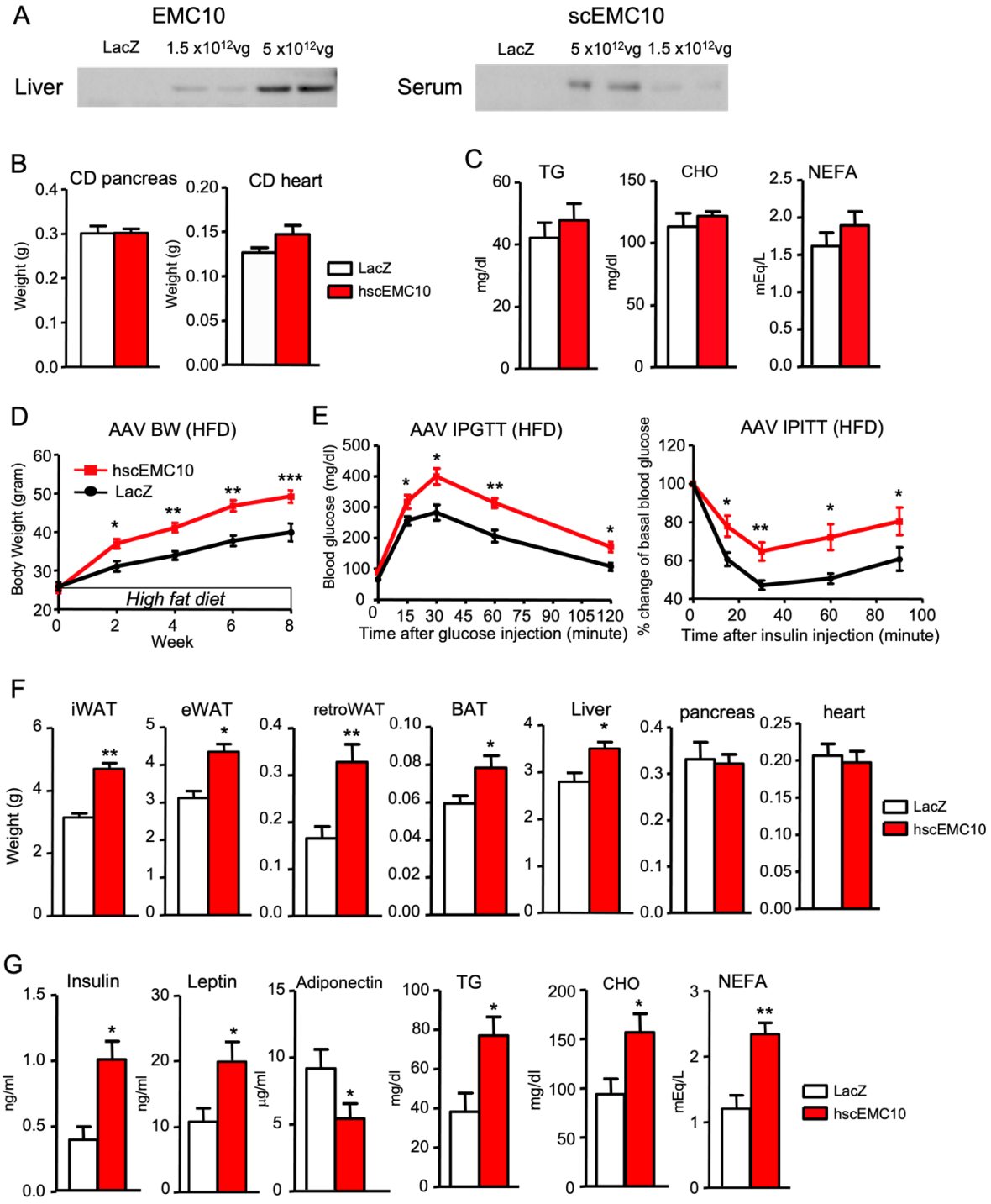
Supplementary Figure 5



Supplementary Figure 5. Phenotypes of *Emc10* knockout mice fed with high fat diet (HFD)

(A) Percentage of body composition, body length and kidney weight of male WT (open), and KO (red) mice fed with 12-wks of HFD (n=6-8 per group). **(B)** Representative images of hematoxylin and eosin (H&E)-stained sections of visceral (epididymal, eWAT), subcutaneous (inguinal, iWAT), and brown (BAT) white adipose tissue from male WT and KO mice fed HFD. **(C)** Quantification of eWAT and iWAT adipocyte size from male WT (black square) and KO (red circle) mice fed HFD. **(D)** *Mcp-1*, *Tnfa*, and *F4/80* mRNA in eWAT from male WT (open), and KO (red) mice fed with 12-wks of HFD (n=6-8 per group). All data are presented as mean +/- SEM. *, $p<0.05$; **, $p<0.01$.

Supplementary Figure 6

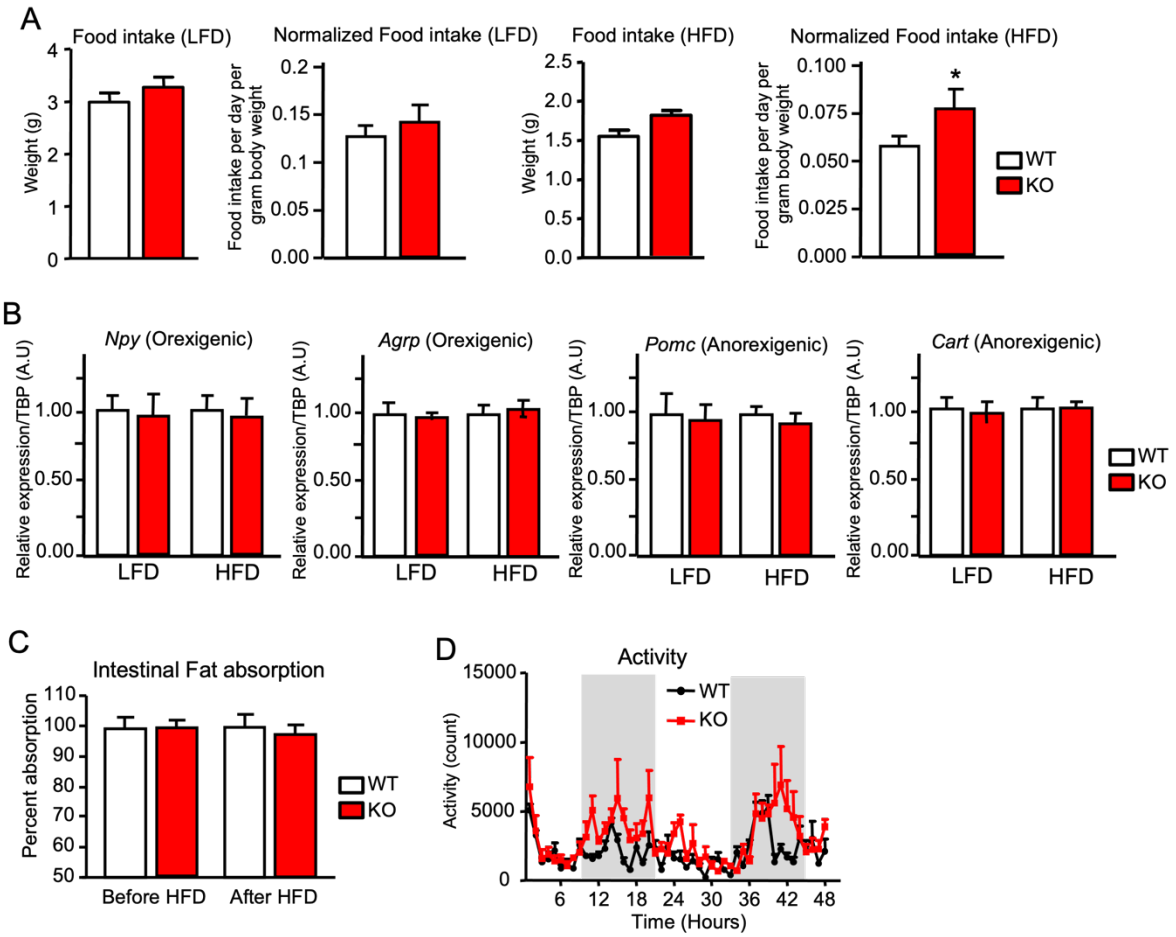


Supplementary Figure 6. Phenotypes of *hscEMC10* overexpressed mice

(A) Representative western blotting for EMC10 protein in liver and serum from C57BL/6 mice after injected with AAV-LacZ or AAV-*hscEMC10*. **(B)** Pancreas and heart weights of C57BL/6 mice fed with 18-wks of chow diet (CD) after injection with AAV-LacZ or AAV-*hscEMC10* (n=6-8 per group). **(C)** Plasma triglyceride (TG), cholesterol (CHO) and non-esterified fatty acid (NEFA) of C57BL/6 mice fed with 18-wks of CD after injection with AAV-LacZ or AAV-*hscEMC10* (n=6-8 per group). **(D)** Body weights of male C57BL/6 mice expressing LacZ control or *hscEMC10* via tail-vein AAV transduction after 8-wks of HFD (n=6 per group). **(E)** Glucose tolerance (left) and insulin tolerance (right) of male C57BL/6 mice expressing

LacZ control or *hscEMC10* via tail-vein AAV transduction after 8-wks of HFD (n=6 per group). **(F)** Weights of subcutaneous (inguinal, iWAT), visceral (epididymal, eWAT), retroperitoneal (retroWAT) and brown (BAT) adipose tissue, and liver, pancreas, and heart of male C57BL/6 mice expressing LacZ control or *hscEMC10* via tail-vein AAV transduction after 8-wks of HFD (n=6 per group). **(G)** Plasma insulin, leptin, adiponectin, TG, CHO, and NEFA of male C57BL/6 mice in the fed state expressing LacZ control or *hscEMC10* via tail-vein AAV transduction after 8-wks of HFD (n=6 per group). All data are presented as mean +/- SEM. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

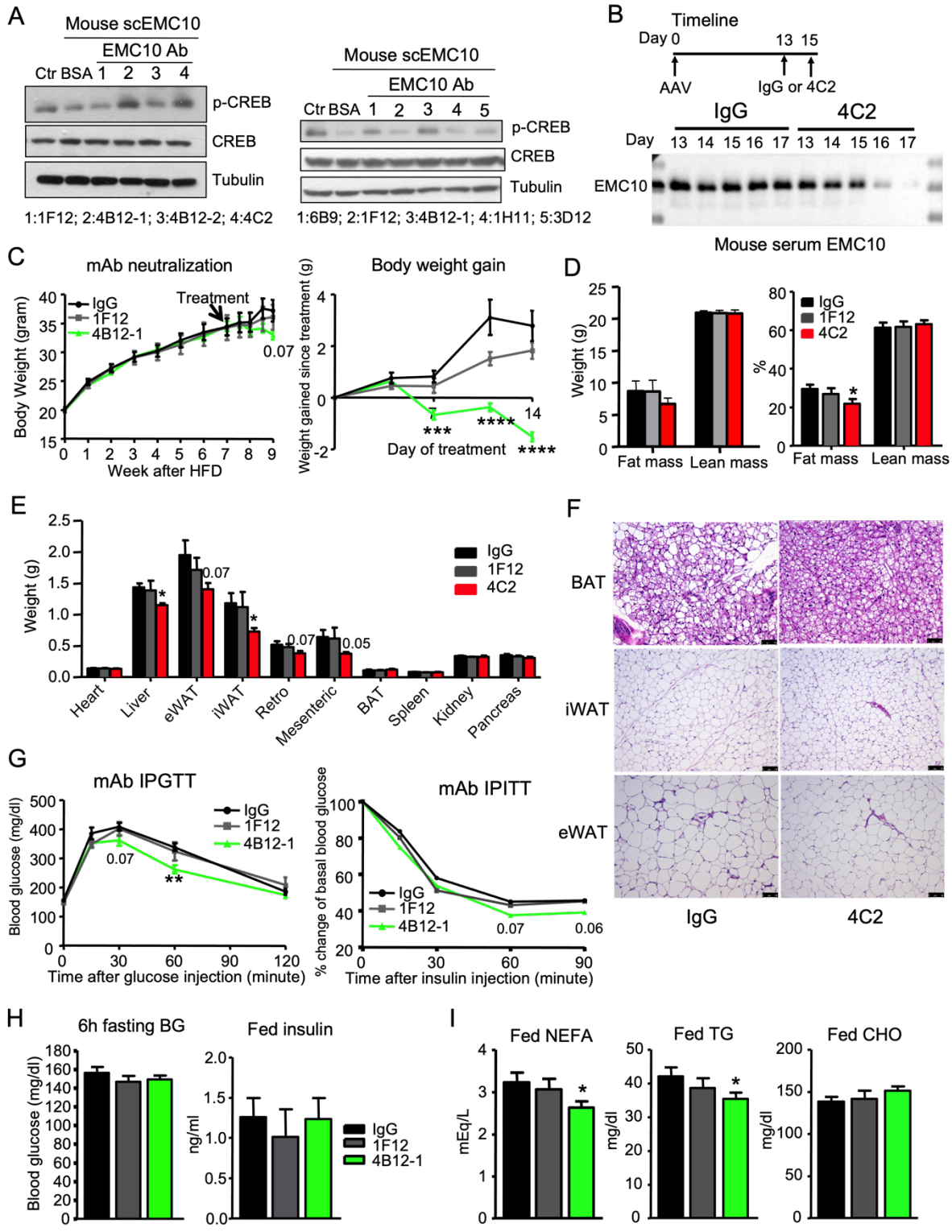
Supplementary Figure 7



Supplementary Figure 7. Energy metabolism of wildtype (WT) and *Emc10* knockout (KO) mice

(A) Food intake and body weight-normalized food intake of male WT (open), and KO (red) mice fed with 12-wks of LFD or HFD (n=6-8 per group). **(B)** Orexigenic and anorexigenic peptide mRNA expression in hypothalamus from male WT (open), and KO (red) mice fed with 12-wks of LFD or HFD (n=6-8 per group). **(C)** Intestinal fat absorption of male WT (open), and KO (red) mice before or fed with 12-wks of HFD (n=6-8 per group). **(D)** Physical activity of male WT (circle, black), and KO (square, red) mice fed with 12-wks of HFD (n=6-8 per group). All data are presented as mean +/- SEM. *, $p<0.05$.

Supplementary Figure 8



Supplementary Figure 8. Phenotypes of mice treated with scEMC10 monoclonal antibodies

(A) Western blotting for phospho (Ser 133)-CREB, total CREB and tubulin in HeLa cells treated with media containing 1 μg/ml mouse scEMC10 protein and 1 μg/ml individual mouse anti-human scEMC10 monoclonal antibody or BSA as indicated for 6 h, Ctr: Control medium without mouse scEMC10 protein nor antibodies. **(B)** Western blotting for scEMC10 in serum from *scEmc10* over-expressor mice before and

after treatment with either IgG or 4C2 antibodies. **(C)** Body weight (left) and body weight gain (right) of C57BL/6J male mice fed with HFD before or after IP injected with 3 mg/kg BW antibody as indicated twice a week. (IgG, black circle. mAb-1F12, grey square. mAb-4B12-1, green triangle) (n = 8-10 per group). **(D)** Body composition of mice IP injected with IgG (black), 1F12 (grey) or 4C2 (red) antibodies determined by DEXA (n=8-10 per group). **(E)** Tissue {heart, liver, eWAT, iWAT, retroperitoneal (Retro) and mesenteric adipose tissue, BAT, spleen, kidney, pancreas} weight from male mice treated with IgG (black), 1F12 (grey) or 4C2 (red) antibodies (n=8-10 per group). **(F)** Representative images of H&E-stained sections of BAT, iWAT and eWAT from mice treated with IgG or 4C2 antibodies. **(G)** Glucose tolerance (left) and insulin tolerance (right) of mice treated with IgG (black circle), 1F12 (grey square) or 4B12-1 (green triangle) antibodies (n=8-10 per group). **(H)** Plasma glucose after 6h fasting and fed insulin in male mice treated with IgG (black), 1F12 (grey) or 4B12-1 (green) antibodies (n=8-10 per group). **(I)** Fed plasma non-esterified fatty acid (NEFA), triglyceride (TG), and cholesterol (CHO) in mice treated with IgG (black), 1F12 (grey) and 4B12-1 (green) antibodies (n=8-10 per group). All data are presented as mean +/- SEM. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$.