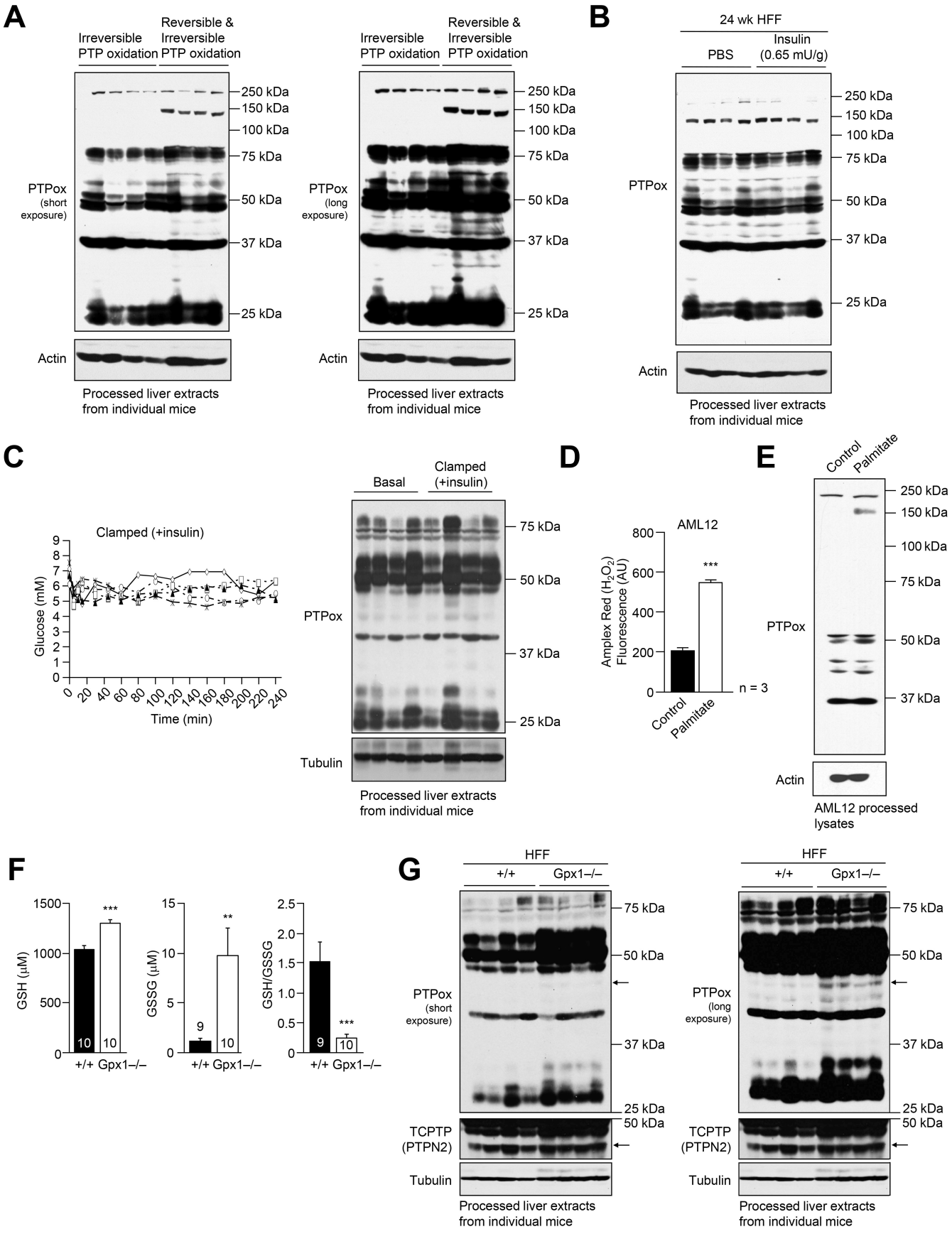
SUPPLEMENTAL INFORMATION



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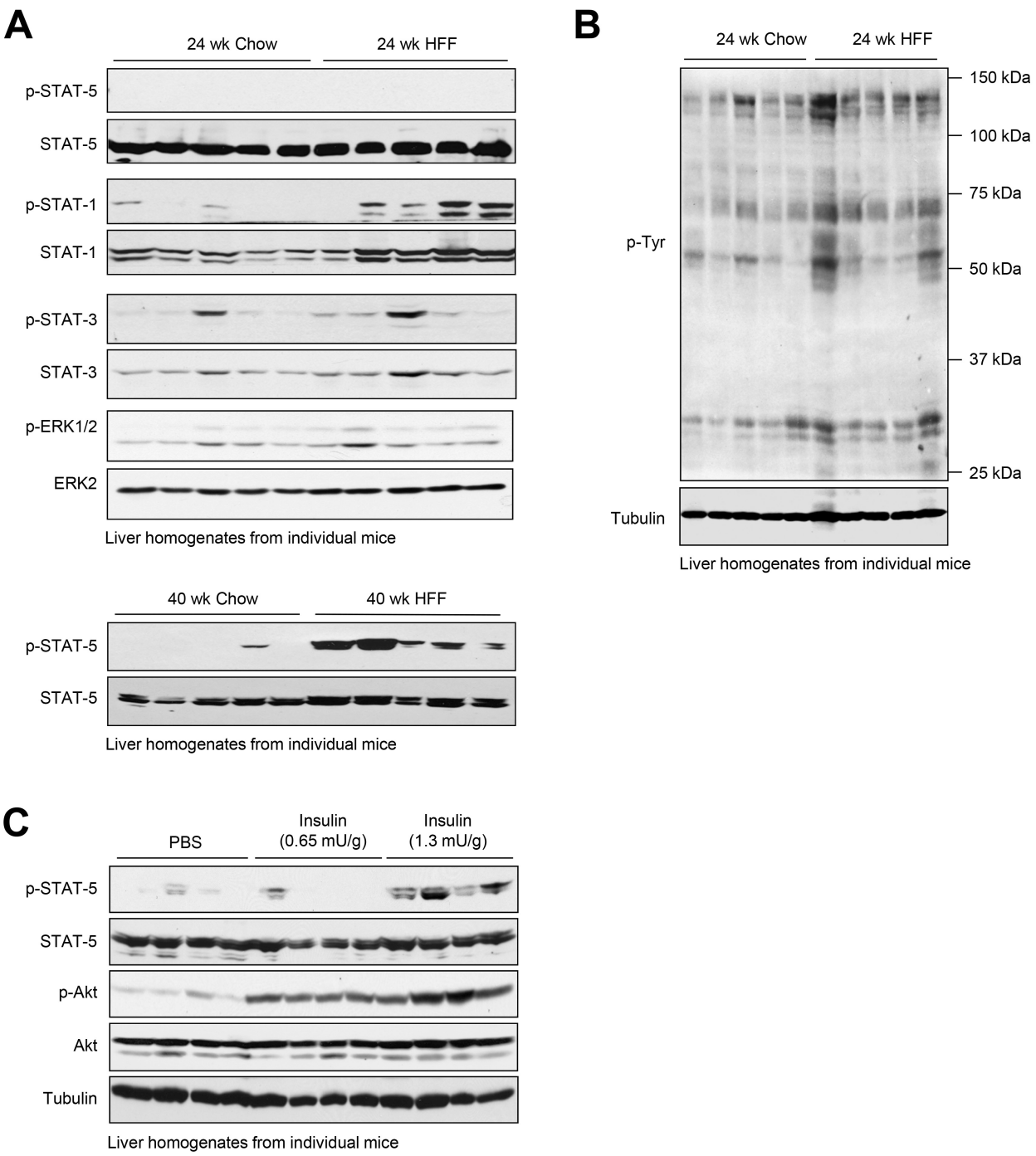
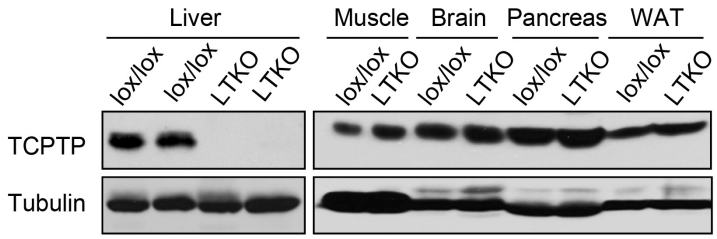
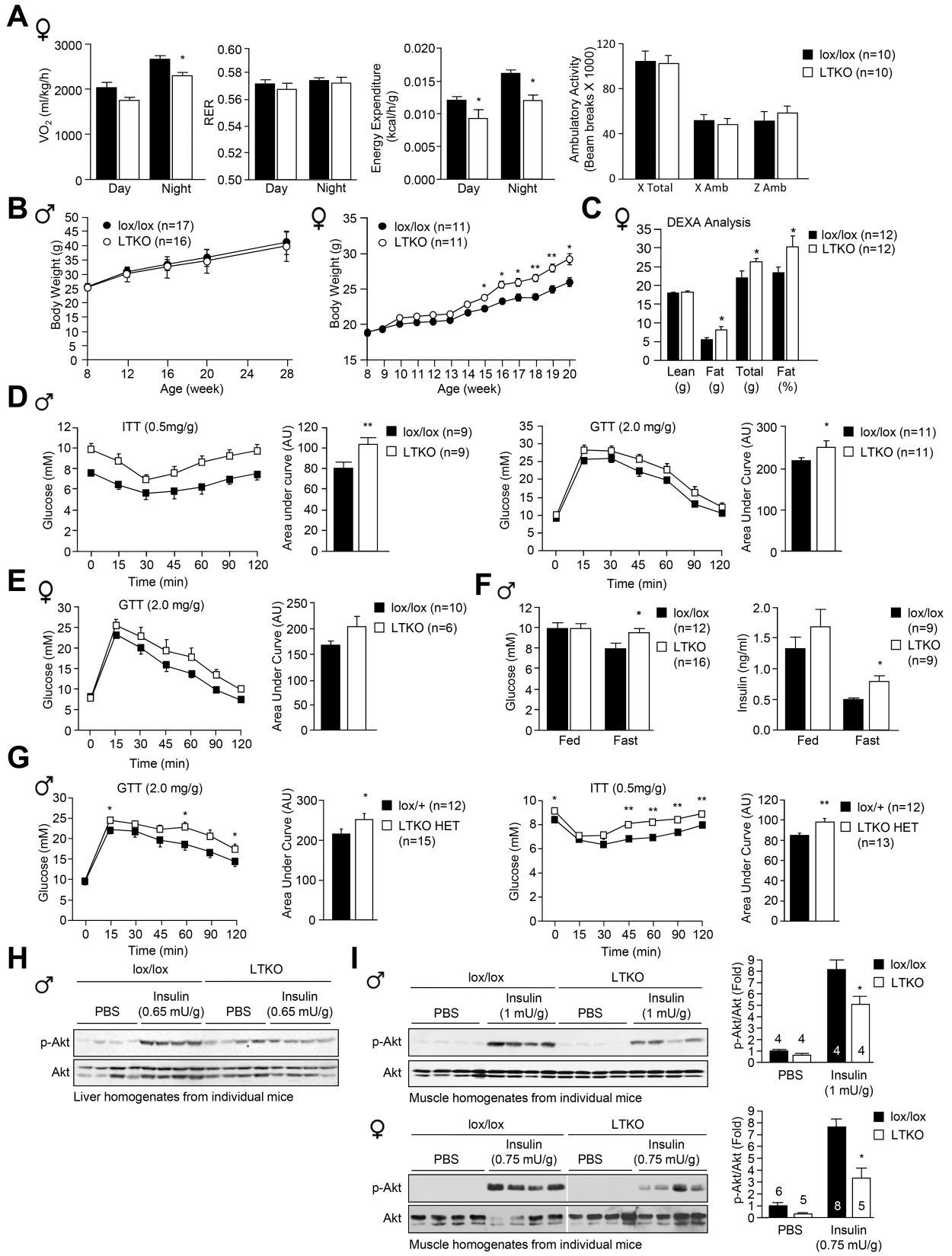
Supplementary Figure 1, related to Figures 1 and 2. Hepatic PTP oxidation. **(a)** Eight week-old male C57BL/6 mice were HFF for 24 weeks and livers isolated and homogenised in the presence of NEM. The clarified extracts were resolved by SDS-PAGE and immunoblotted with the PTPox antibody to monitor for irreversible PTP oxidation ($-SO_3H$), or otherwise processed for the detection of total (reversible and irreversible PTP oxidation; as described in Material and Methods) and then subjected to SDS-PAGE and immunoblotting with the PTPox antibody. **(b)** Eight week-old male C57BL/6 mice were HFF for 24 weeks, fasted and then injected with PBS or insulin (0.65 mU insulin/g body weight, 10 min) and livers extracted and processed for an assessment of total PTP oxidation by immunoblotting with the PTPox antibody. (**c**) Twenty week-old male C57BL/6 mice were fasted overnight and subjected to hyperinsulinemic euglycemic clamps (60 mU/ml insulin infused at 20-40 μl/min and fasted blood glucose levels maintained by the co-infusion of 5% w/v glucose). Blood glucose levels in individual clamped mice are shown. Livers were extracted and processed for an assessment of total PTP oxidation by immunoblotting with the PTPox antibody. (**d-e**) AML hepatocytes were either left untreated or treated with 0.5 mM palmitate-BSA overnight and (**d**) H_2O_2 production measured in live cells using Amplex Red and normalised to total protein, or (**e**) processed for an analysis of total PTP oxidation and immunoblotted with PTPox. (**f-g**) Ten week-old male Gpx1+/+ and Gpx1–/– mice were HFF for 24 weeks and (**f**) whole blood GSH, GSSG and GSH/GSSG ratios determined and (**g**) livers extracted and processed for an assessment of total PTP oxidation by immunoblot analysis with the PTPox antibody. Results shown in (**d, f**) are means ± SEM for the indicated number of mice and are representative of at least two independent experiments. Significance was determined using 2-tailed student's t-test; **p<0.01, ***p<0.001.



Supplementary Figure 2, related to Figure 2. Hepatic STAT-1, STAT-3 and STAT-5 signaling. **(a-b)** Eight week-old male C57BL/6 mice were chow fed or high fat-fed (HFF) for 24 or 40 weeks as indicated and livers extracted from fasted (4h) mice and processed for immunoblotting. (**c**) Eight week-old male C57BL/6 chow fed mice were fasted for 6 h and injected with PBS or insulin (0.65-1.3 mU/g,10 min) and livers extracted and processed for immunoblot analysis with the indicated antibodies.



Supplementary Figure 3, related to Figure 3. Generation of LTKO mice. Tissue homogenates from *Ptpn2*$^{lox/lox}$ (lox/lox) and *Alb*-Cre;*Ptpn2*$^{lox/lox}$ (LTKO) mice were processed for immunoblotting to monitor for TCPTP deletion. Representative results are shown.



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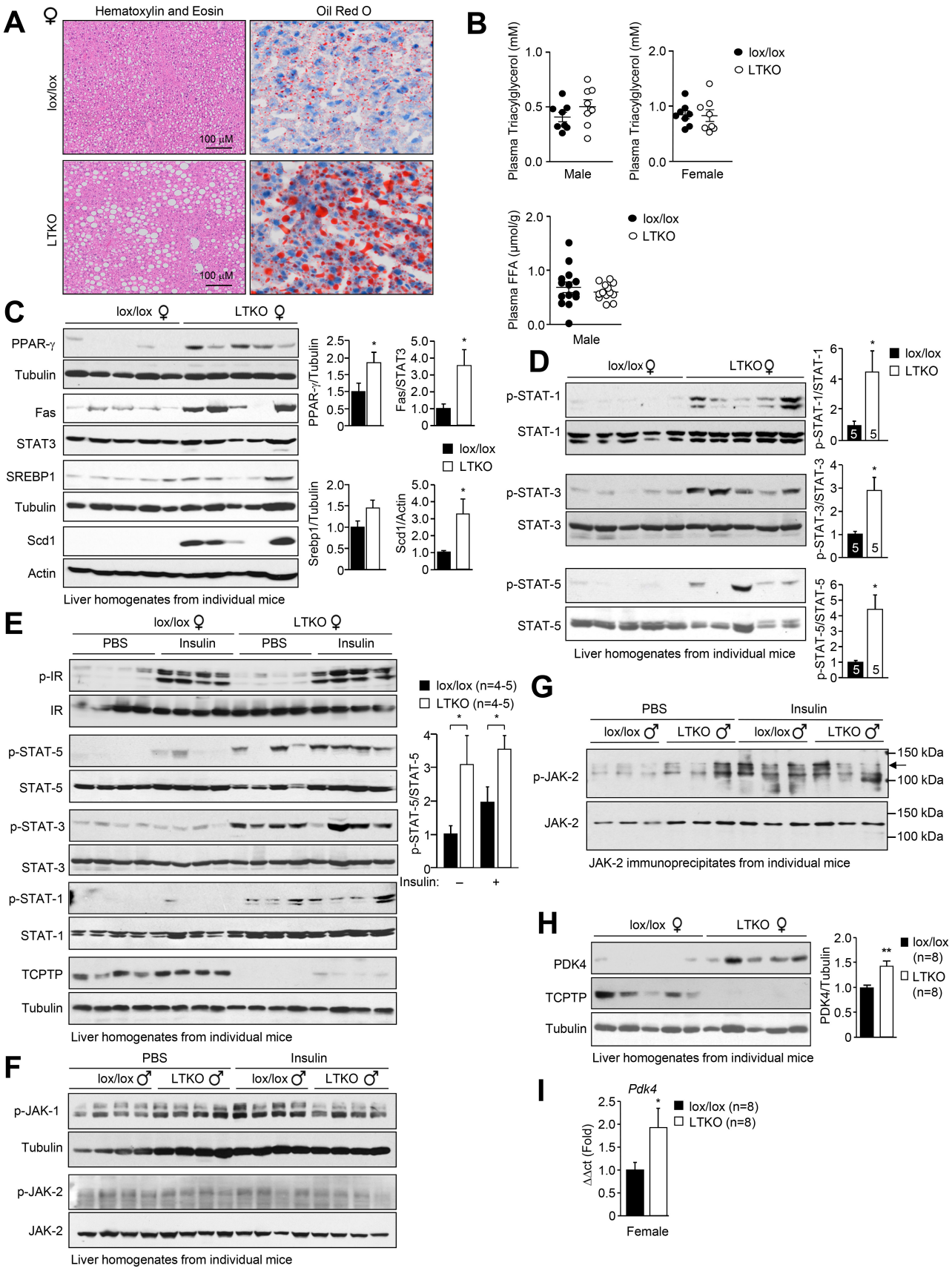
Supplementary Figure 4, related to Figure 3. HFF LTKO and LTKO HET mice exhibit decreased energy expenditure, insulin resistance and glucose intolerance. **(a)** Seven week-old female lox/lox control and LTKO mice were HFF for 12 weeks and day and night oxygen consumption, respiratory exchange ratios (RER= VO_2/VCO_2), energy expenditure and ambulatory activity were assessed using a Comprehensive Lab Animal Monitoring System (CLAMS) fitted with open circuit indirect calorimetry and activity monitors. (**b**) Eight week-old male versus female lox/lox control and LTKO mice were fed a standard chow diet and weekly body weight monitored. (**c**) Body composition (as assessed by DEXA) in 20 week-old female mice fed a chow diet. (**d, e, g**) Seven week-old male versus female lox/lox and LTKO mice, or *Ptpn2*$^{lox/+}$ (lox/+) and *Alb*-Cre;*Ptpn2*$^{lox/+}$ (LTKO HET) were HFF for 12 weeks and 20 weeks respectively. HFF mice were subjected to insulin tolerance tests (0.5 mU/g) or glucose tolerance tests (2 mg/g); areas under curves were determined and arbitrary units (AU) are shown. (**f**) Seven week-old male lox/lox and LTKO mice were HFF for 12 weeks and fed and fasted blood glucose and plasma insulin levels determined. (**h-i**) Seven week-old male versus female lox/lox and LTKO mice were HFF for 12 weeks, fasted for 6 h and then injected with PBS or insulin (0.65-1.0 mU/g, 10 min). *Gastrocnemius* muscle or livers were extracted and processed for immunoblotting; representative and quantified results are shown. Results shown are means ± SEM; significance was determined using 2-tailed student's t-test; *$p<0.05$, **$p<0.01$.



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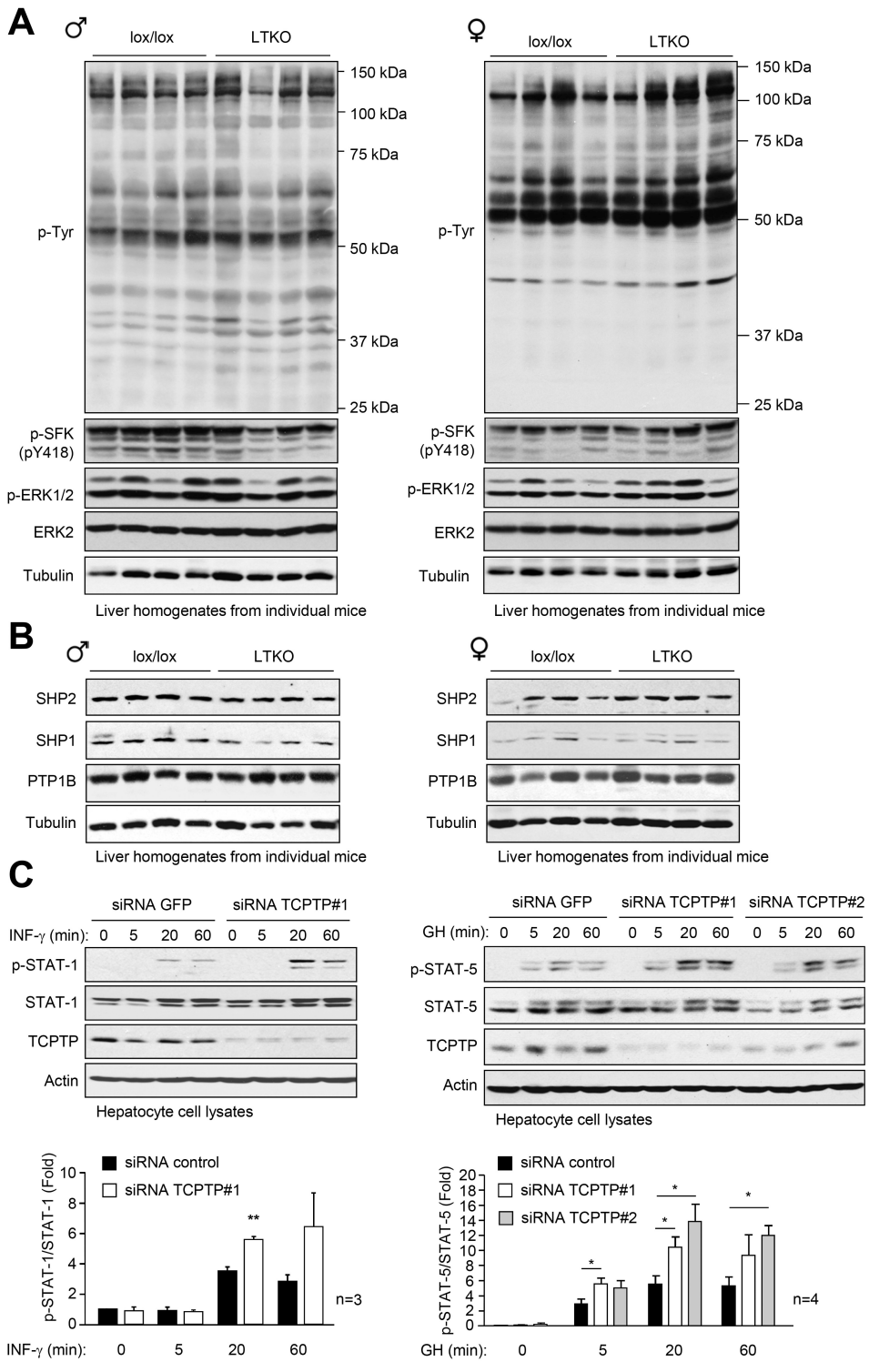
Supplementary Figure 5, related to Figures 4 and 5. HFF LTKO mice exhibit increased hepatic STAT-1, STAT-3 and STAT-5 signaling, PPARγ, Fas, Scd1 and PDK4 expression and steatosis. Seven week-old female lox/lox and LTKO mice were HFF for 12 weeks. (**a**) Livers were extracted and fixed in formalin or frozen in OCT and processed for histological assessment (stained with hematoxylin and eosin staining and Oil Red O respectively). (**b**) Fed plasma triacylglycerol and free fatty acid (FFA) levels were determined. (**c-d**) Livers were extracted from fasted (4 h) mice and processed for immunoblot analysis. (**e**) Mice were fasted for 4 h and injected with PBS or insulin (0.75 mU/g, 10 min) and livers extracted and processed for immunoblot analysis. (**f-g**) Seven week-old male lox/lox and LTKO mice were HFF for 12 weeks, fasted and injected with PBS or insulin (1 mU/g, 10 min) and livers extracted and processed for (**f**) immunoblotting or (**g**) JAK-2 immunoprecipitation and immunoblotting. (**h-i**) Seven week-old female lox/lox and LTKO mice were HFF for 12 weeks, fasted for 4 h and livers extracted and processed for (**h**) immunoblot analysis or (**i**) quantitative (ΔΔCt) real time PCR to monitor for the expression of *Pdk4*. Results shown are means ± SEM; significance was determined using 2-tailed student's t-test; *$p<0.05$, **$p<0.01$.



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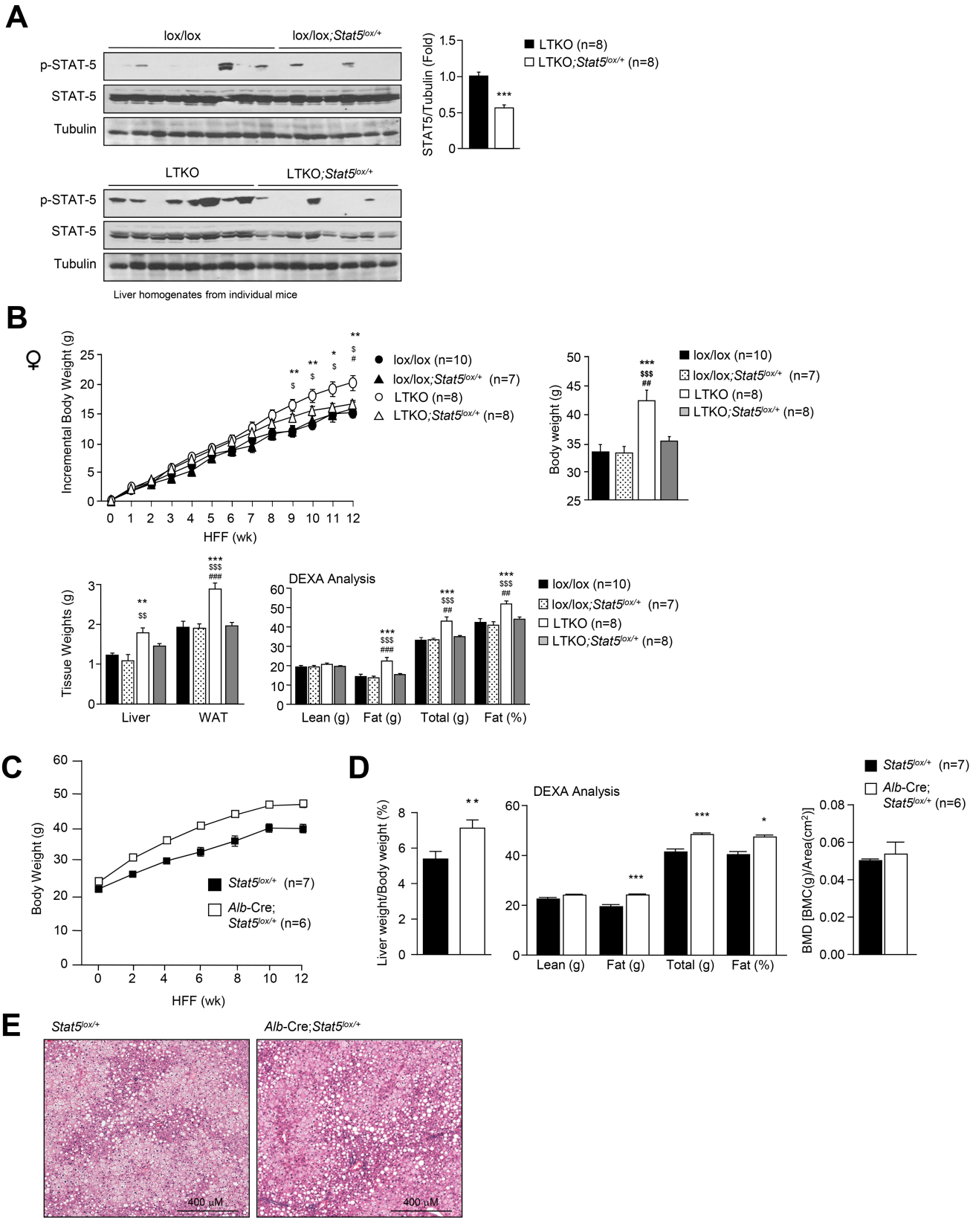
Supplementary Figure 6, related to Figure 5. Tyrosine phosphorylation-dependent signaling is not altered in general in HFF LTKO mice. **(a-b)** Seven week-old male versus female lox/lox and LTKO mice were HFF for 12 weeks, fasted for 4 h and livers extracted and processed for immunoblot analysis. (**c**) Primary hepatocytes were isolated from chow fed C57BL/6 mice and transfected with *GFP* control or *Ptpn2*-specific siRNAs and 48 h later serum starved for 6 h and stimulated with 50 U/ml IFN-γ or 200 ng/ml GH for the indicated times and processed for immunoblot analysis. Quantified results are means ± SEM; significance was determined using 2-tailed student's t-test; *$p<0.05$, **$p<0.01$.



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Supplementary Figure 7, related to Figure 6. STAT-5 heterozygosity corrects the obesity phenotype in HFF LTKO mice. Seven week-old female lox/lox, *Ptpn2*$^{lox/lox}$;*Stat5*$^{lox/+}$ (lox/lox;*Stat5* $^{lox/+}$), LTKO mice, and *Alb*-Cre;*Ptpn2*$^{lox/lox}$;*Stat5*$^{lox/+}$ (LTKO;*Stat5*$^{lox/+}$) mice were HFF for 12 weeks. (**a**) Liver homogenates were processed for immunoblotting and STAT-5 levels quantified and normalised to tubulin. Quantified results are means ± SEM and significance was determined using 2-tailed student's t-test; ***p<0.001. (**b**) Body and tissue weights were determined and body composition assessed by DEXA. Results shown are means ± SEM; significance was determined using a one-way ANOVA; * LTKO versus lox/lox, $ LTKO versus lox/lox;*Stat5* $^{lox/+}$, # LTKO versus LTKO;*Stat5*$^{lox/+}$; *$^{,\$,\#}$p<0.05, **$^{,\$\$,\#\#}$p<0.01, ***$^{,\$\$\$,\#\#\#}$p<0.001. (**c-d**) Seven-week-old male *Stat5*$^{lox/+}$and *Alb*-Cre; *Stat5*$^{lox/+}$ mice were HFF for 12 weeks and body and tissue weights monitored/determined and body composition assessed by DEXA. (**e**) Livers were extracted and processed for histology (hematoxylin and eosin). Quantified results shown are means ± SEM; significance was determined using 2-tailed student's t-test; *p<0.05, **p<0.01, ***p<0.001.