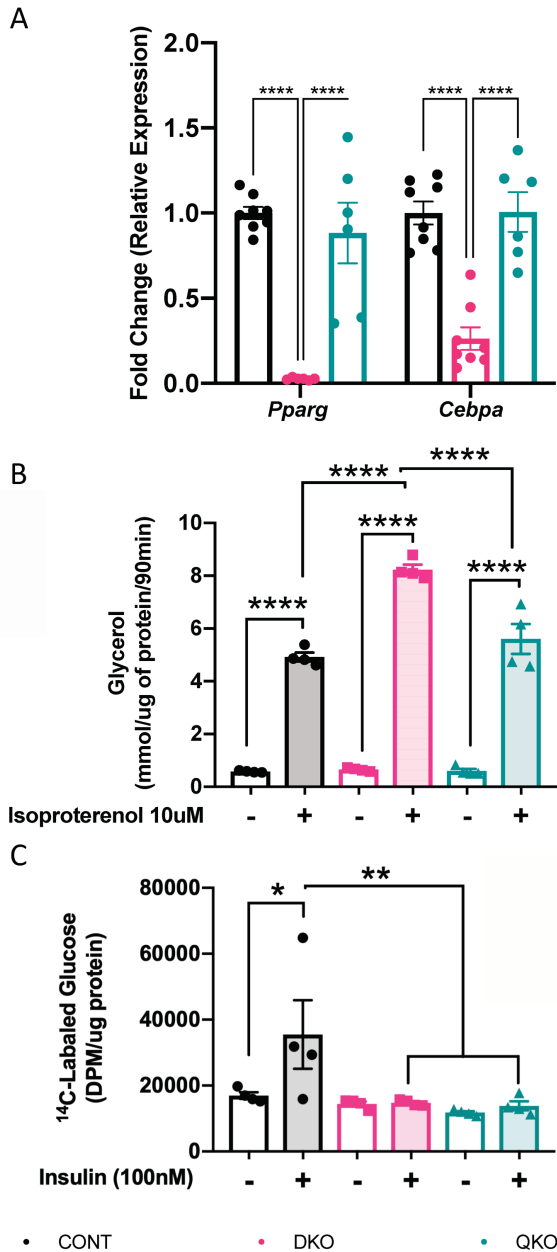
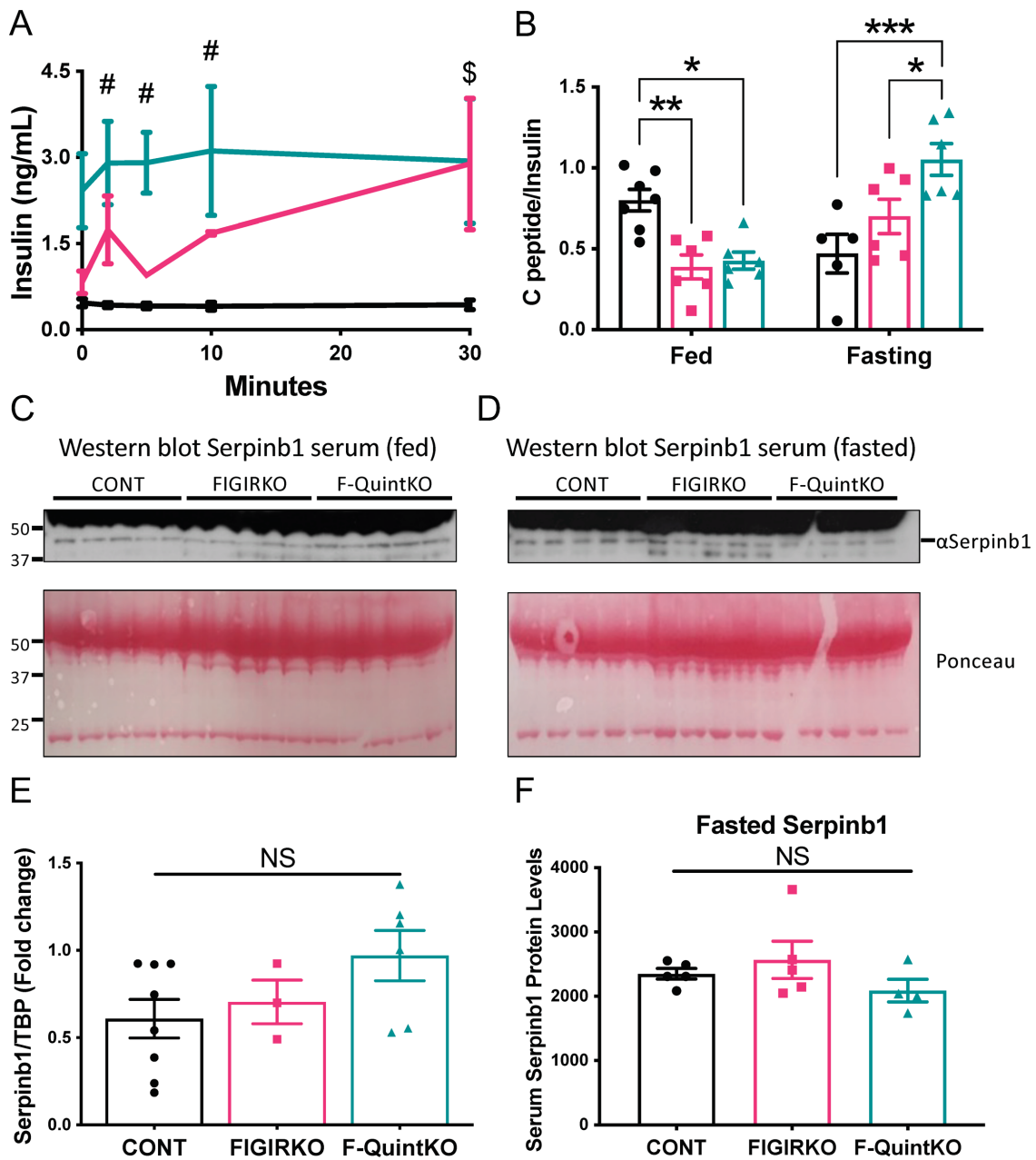


Supplemental Figure 1. F-Quint KO mice are normal at weaning but weight more than CONT by 12-weeks of age. A) Weight of CONT, FIGIRKO, and F-Quint KO mice were measured weekly from weaning (week 4) until 12 weeks of age. Results represent 7-28 mice per group. Statistics were performed using a two-way ANOVA with repeated measures, where a represents $p < 0.05$ between FIGIRKO and CONT or F-Quint KO, b represents $p < 0.05$ between FIGIRKO and F-Quint KO, c represents $p < 0.05$ between CONT and F-Quint KO, and d represents $p < 0.05$ between CONT and FIGIRKO or F-Quint KO. B-C) DEXA analysis assessed total body fat (B) and lean mass (C) in 12-week-old CONT, FIGIRKO, and F-Quint KO mice. Results represent 3-10 mice per group. Statistics were performed using a one-way ANOVA, where $*P < .05$, $**P < .01$, $****P < .0001$

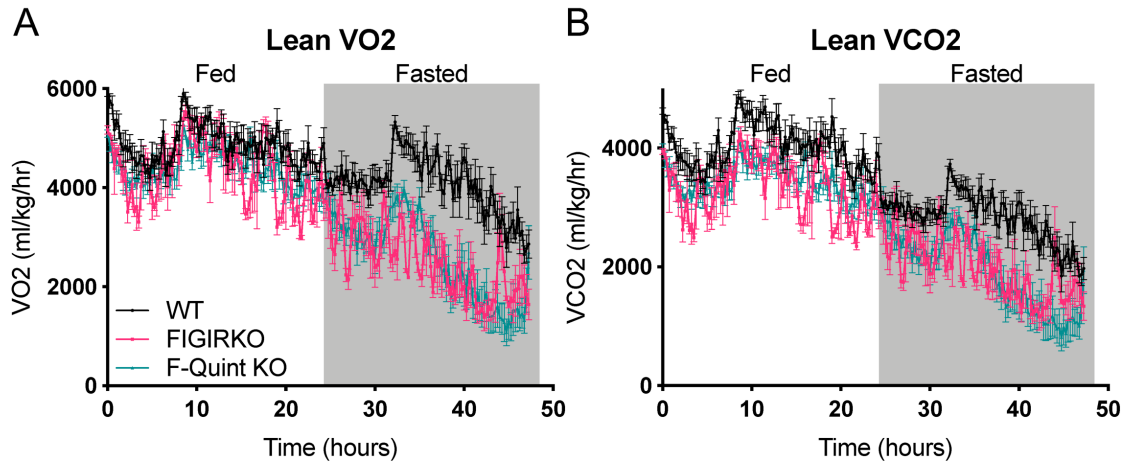


Supplemental Figure 2. Restoration of adipocyte differentiation and function with loss of FOXO1/3/4 in QKO cells. A) mRNA expression of the late adipogenic transcription factors, *Pparg* and *Cebpa*, in CONT, DKO, and QKO preadipocyte cells after differentiation for 4 days. Results represent 6-8 replicates per group. B) Lipolysis rates after stimulation with 10 μ M isoproterenol were measured by glycerol release from adipocytes after 9 days of adipogenic differentiation. Data are shown as mean \pm SEM of 4 replicates and are normalized by lipid content of the cells. C) ¹⁴C-Deoxy-D-glucose uptake in preadipocyte cell lines in the basal state and after pretreatment for 30 min with 100nM insulin. Uptake was measured for 10 minutes and data are shown as mean \pm SEM of 4 samples. Statistics were performed using a one-way ANOVA, where * P < .05, ** P < .01, **** P < .0001

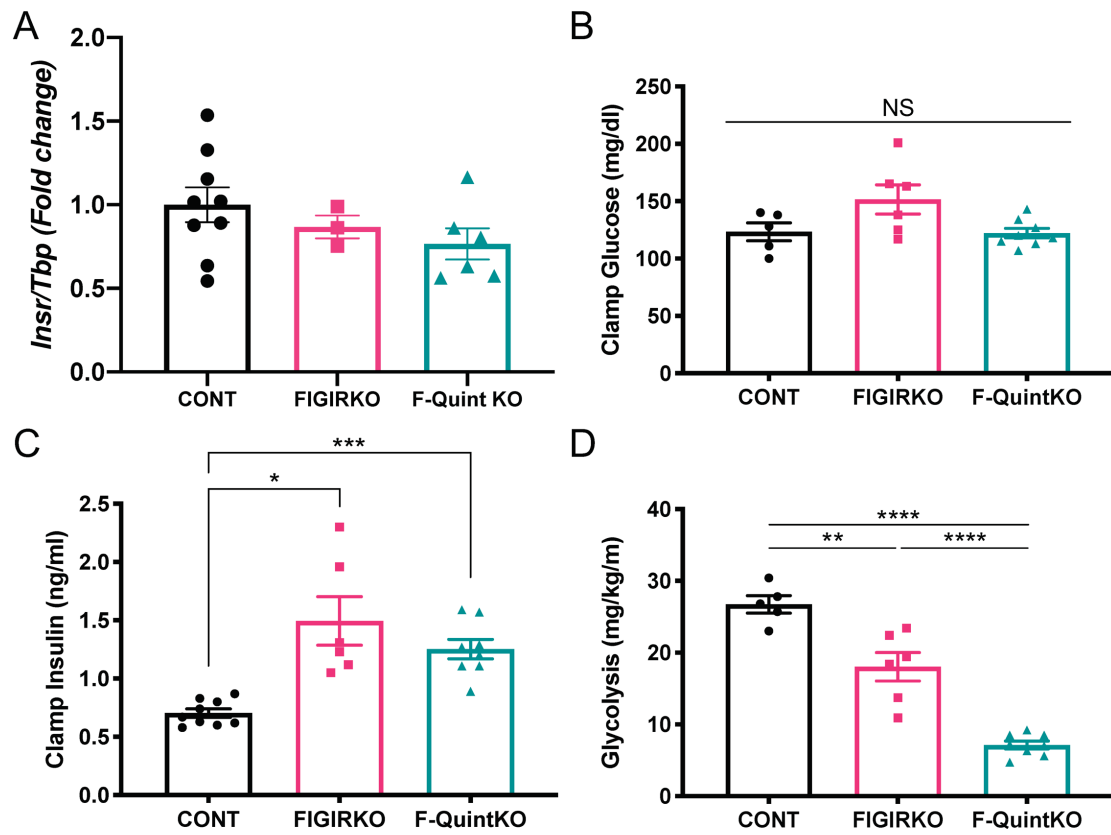


Supplemental Figure 3. β -Cell hyperplasia remains despite loss of FOXO1/3/4 in F-Quint KO mice. A) *In vivo* GSIS in CONT, FIGIRKO, and F-Quint KO mice at 3-months of age. Results represent 3-10 mice per group. Statistics were performed using a two-way ANOVA with repeated measures, where # represents $p < 0.05$ CONT vs F-Quint KO, and \$ represents $p < 0.05$ CONT vs FIGIRKO and CONT vs F-Quint KO. B) Insulin clearance measured by the ratio of C-peptide to insulin was calculated in 3-month-old CONT, FIGIRKO, and F-Quint KO mice in the fed and fasting state. Results represent 6-8 mice per group. Statistics were performed using a one-way ANOVA, where * $P < .05$, ** $P < .01$, and *** $P < .001$. C-D) Western blot of SERPINB1 in fed (C) and fasted (D) serum isolated from 3-month-old CONT, FIGIRKO, and F-Quint KO mice. Line

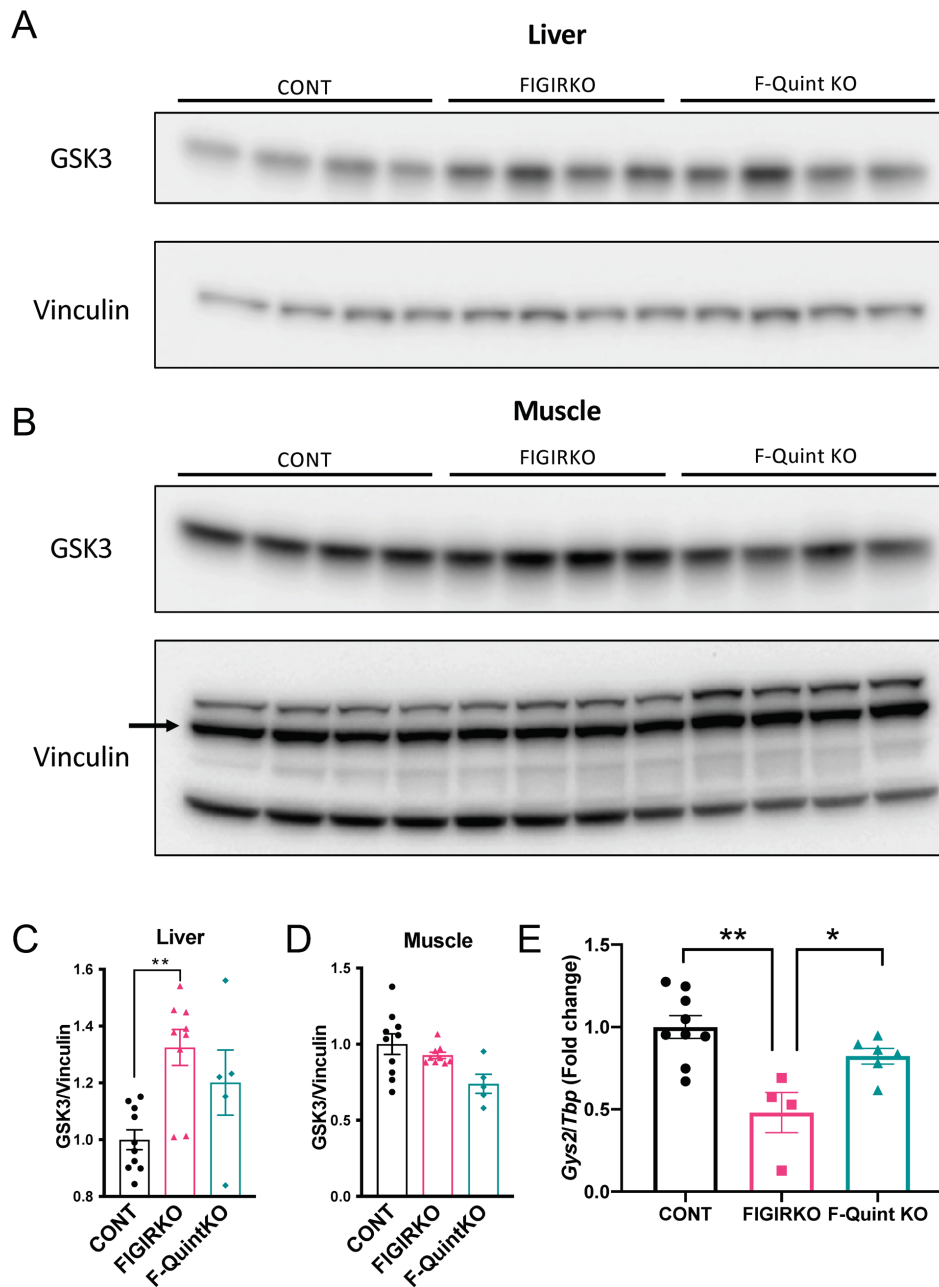
indicates SERPINB1 band. E) mRNA expression of *Serpinb1* relative to *TBP* in liver of 3-month-old random fed CONT, FIGIRKO, F-Quint KO mice. Results represent 4-9 mice per group. Statistics were performed using a one-way ANOVA, where NS represents $p > 0.05$. F) Densitometric quantification of SERPINB1 proteins levels relative to ponceau staining in serum of fasting 3-month-old CONT, FIGIRKO, and F-Quint KO mice. Results represent 4-5 mice per group. Statistics were performed using a one-way ANOVA, where NS represents $p > 0.05$.



Supplemental Figure 4. Improvement in fasted energy expenditure with loss of FOXO1/3/4 in F-Quint KO mice. A-B) O₂ utilization (A) and CO₂ production (B) of 12-week-old CONT, FIGIRKO, and F-Quint KO mice were measured using metabolic cages and normalized to lean body mass. Results represent 3-10 mice per group.

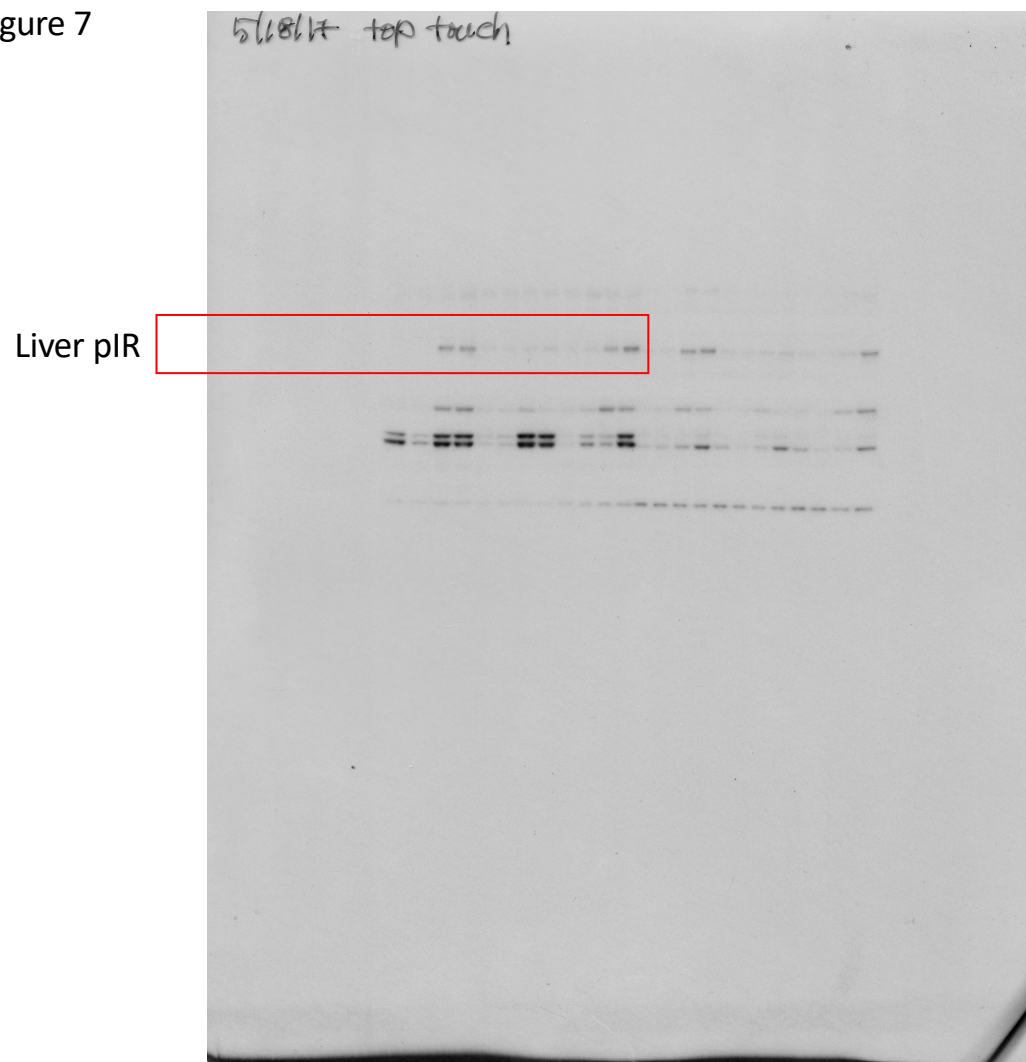


Supplemental Figure 5. Restoration of liver insulin sensitivity in the context of whole-body insulin resistance in F-Quint KO mice. mRNA expression of *Insr* in the livers of chow-fed CONT, FIGIRKO, and F-Quint KO mice at 3-months of age. Results represent 3-10 mice per group. Plasma glucose levels (B), Plasma insulin levels (C), and clamp HGP (D) were measured during a hyperinsulinemic-euglycemic clamp in 3-month old CONT, FIGIRKO, and F-Quint KO mice. Results represent 5-8 mice per group. Statistics were performed using a one-way ANOVA, where * $P < .05$, ** $P < .01$, *** $P < .001$, and **** $P < .0001$.

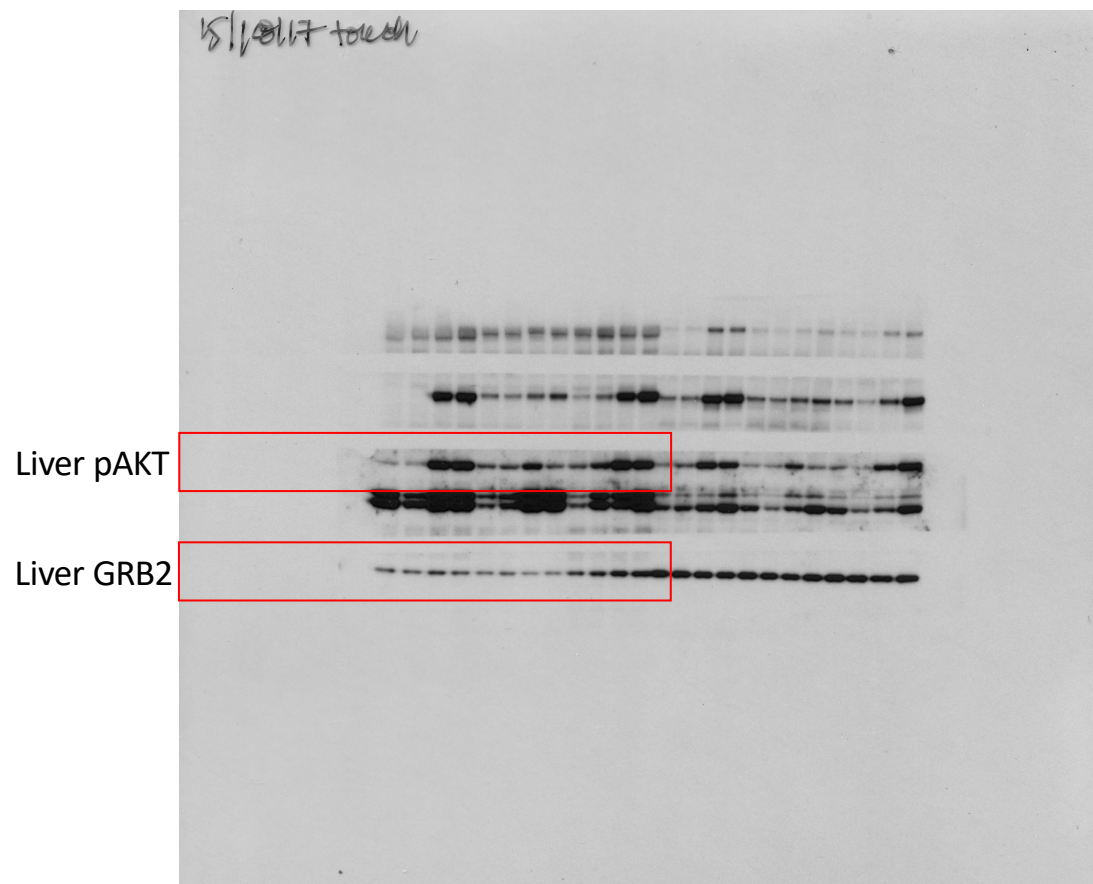


Supplemental Figure 6. Partial restoration of liver GSK3 levels and *Gys2* expression in F-Quint KO mice. A-B) Western blot of GSK3 relative to Vinculin in liver (A) and muscle (B) isolated from 3-month-old CONT, FIGIRKO, and F-Quint KO mice. Line indicates Vinculin band. C-D) Densitometric quantification of GSK3 proteins levels relative to Vinculin in liver (C) and muscle (D) of 3-month-old CONT, FIGIRKO, and F-Quint KO mice. Results represent 4-5 mice per group. E) mRNA expression of *Gys2* relative to *TBP* in liver of 3-month-old random fed CONT, FIGIRKO, F-Quint KO mice. Results represent 4-9 mice per group. Statistics were performed using a one-way ANOVA, where $*P < .05$, $**P < .01$.

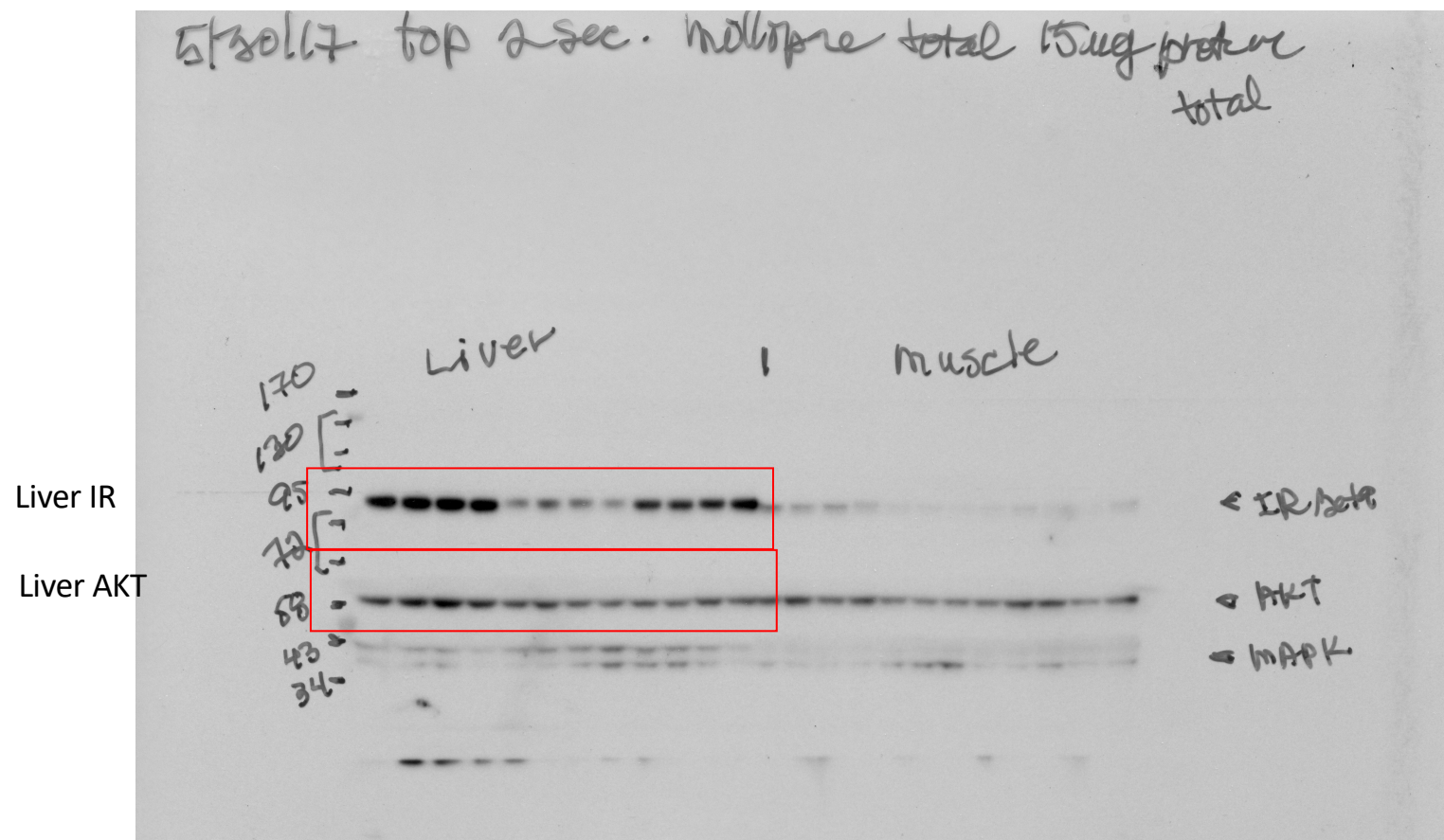
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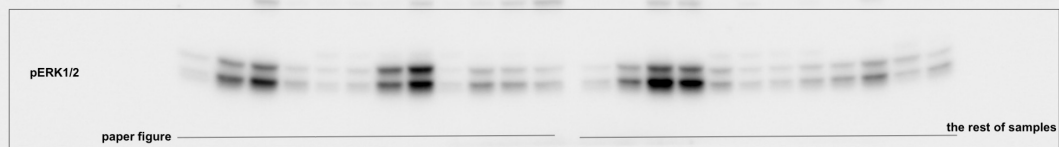


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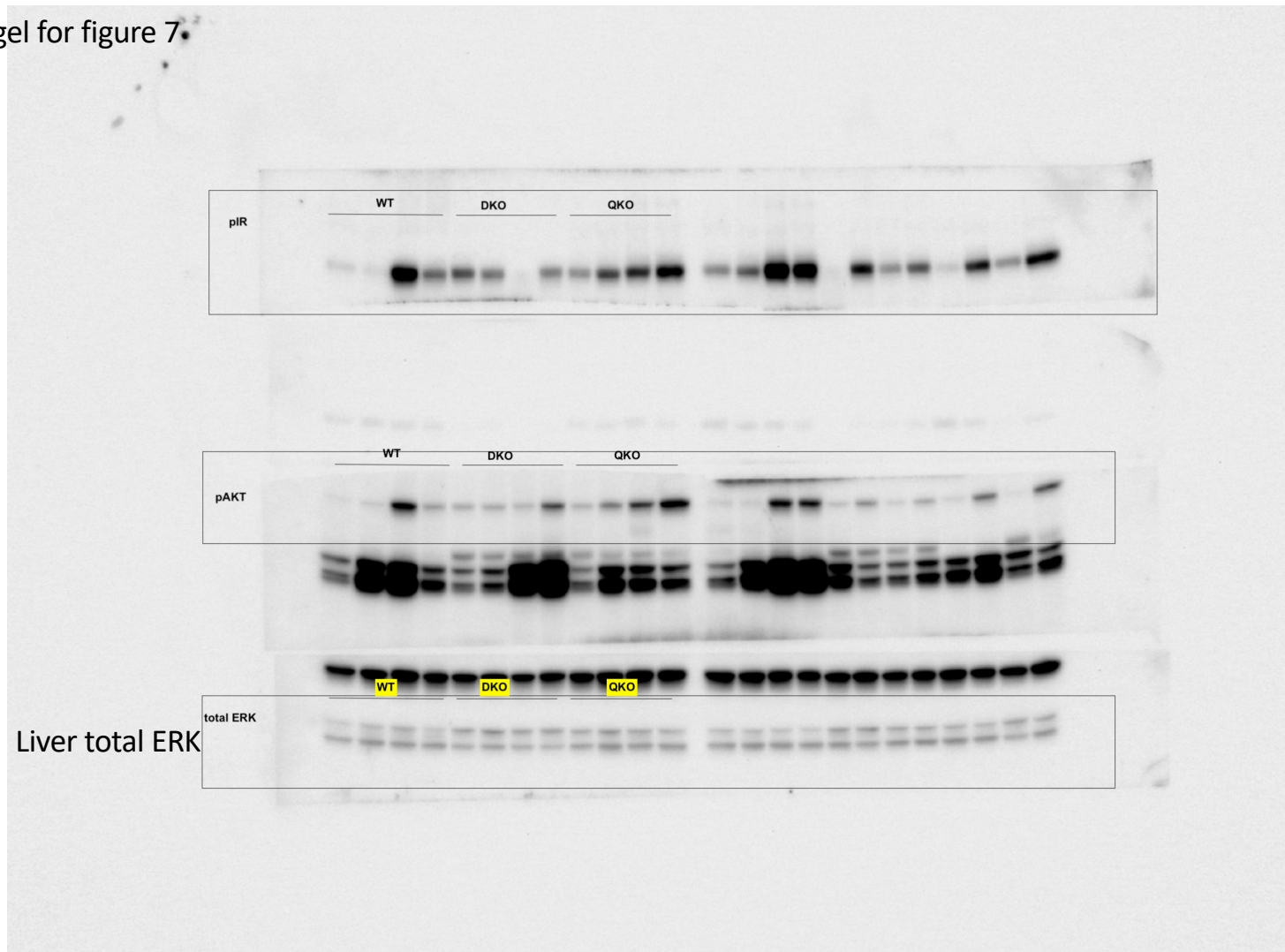


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Liver

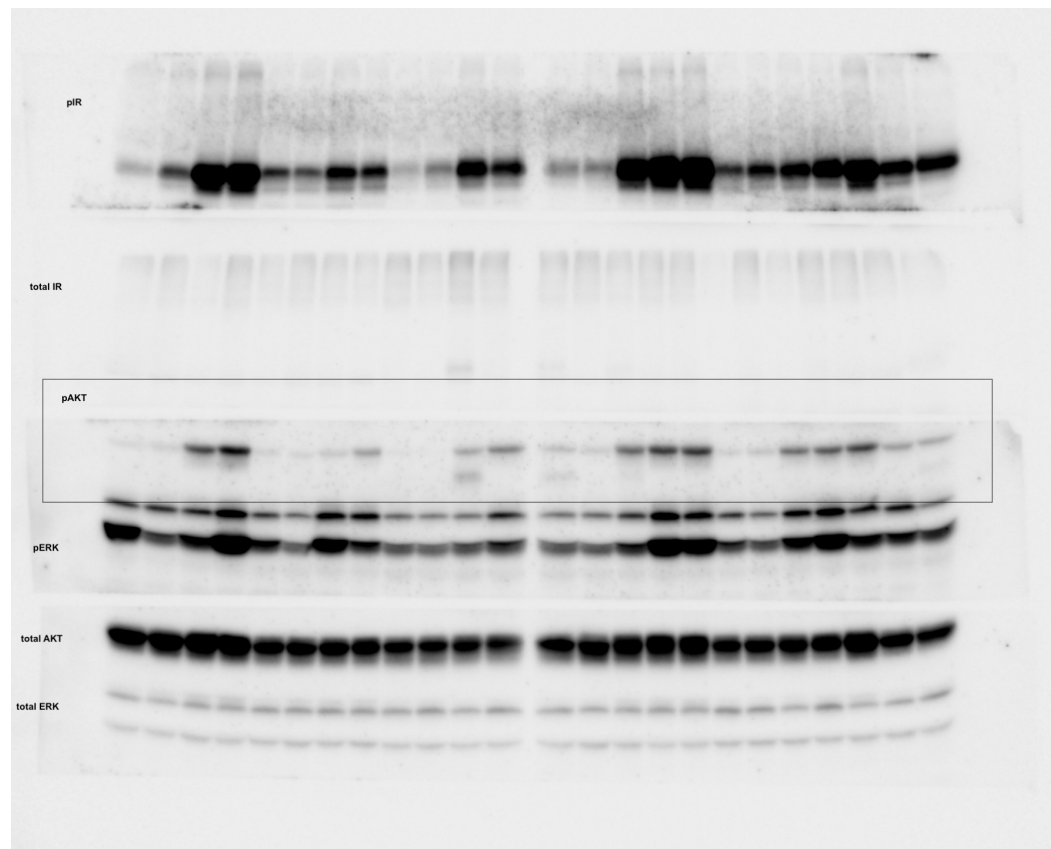


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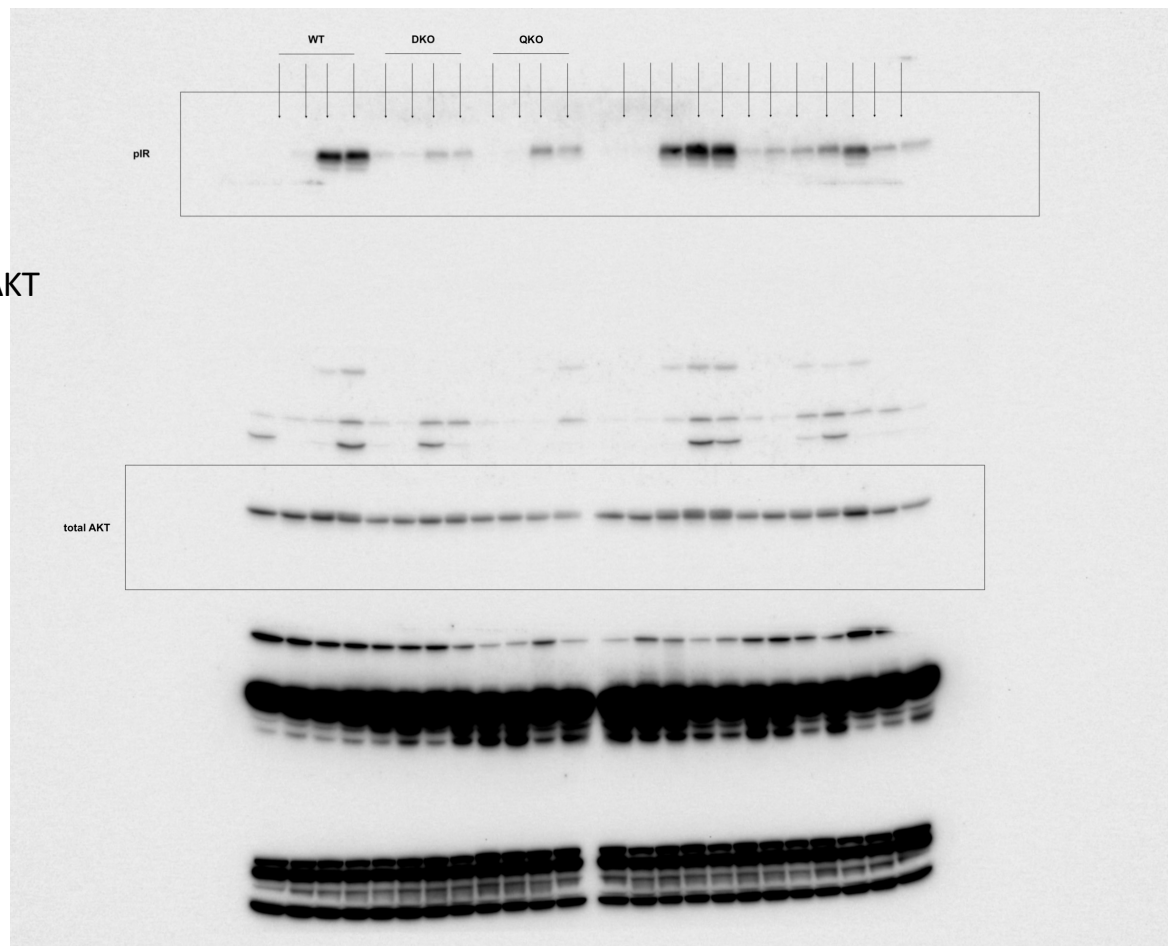


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Muscle pAKT



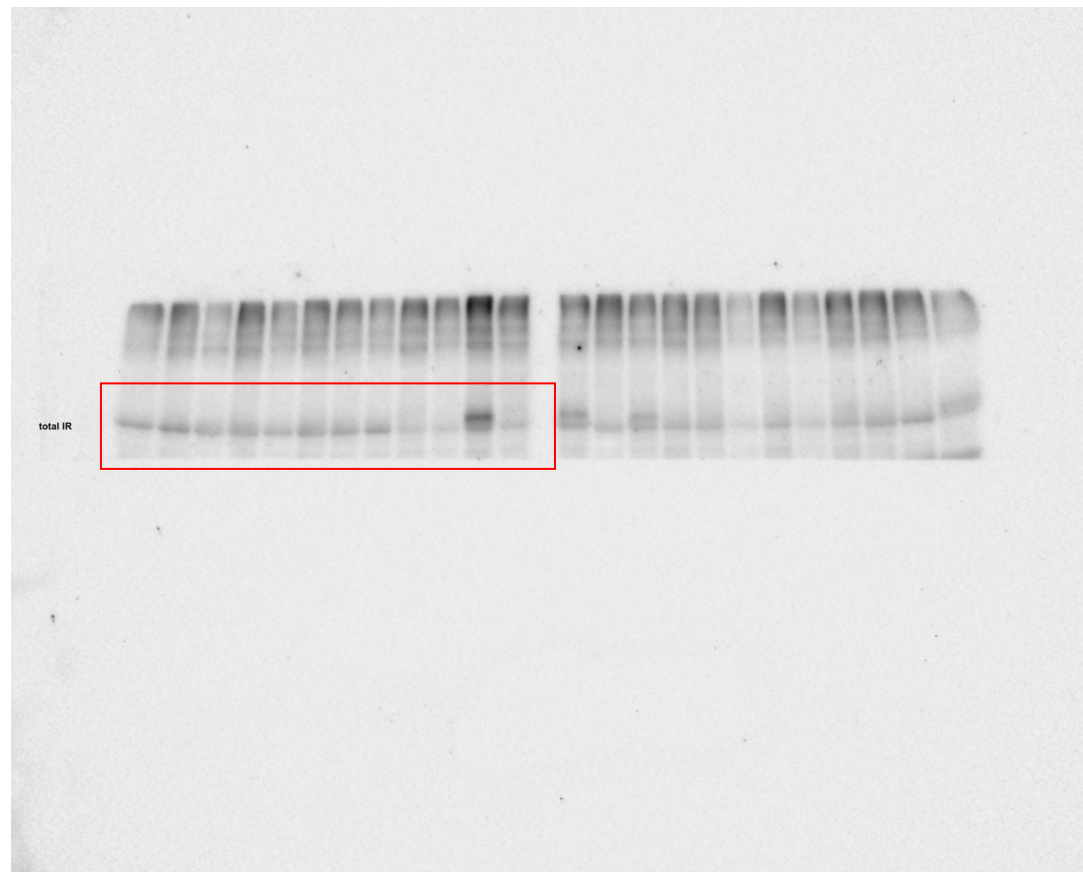
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Muscle pIR and total AKT

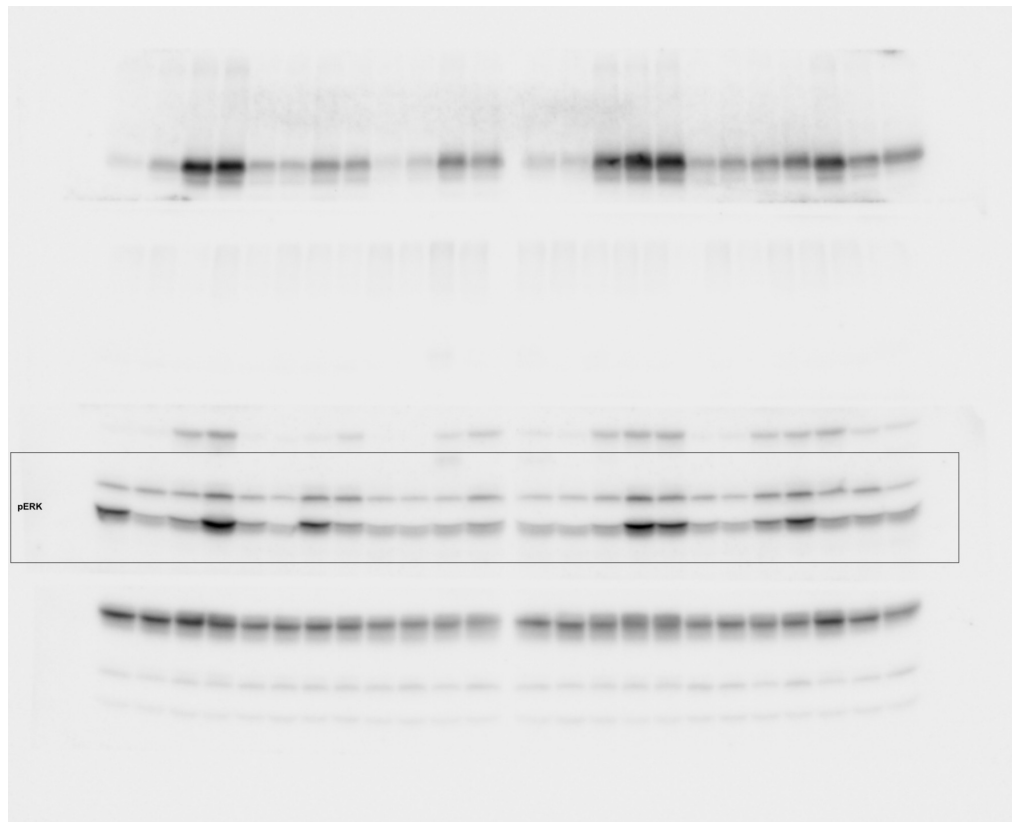
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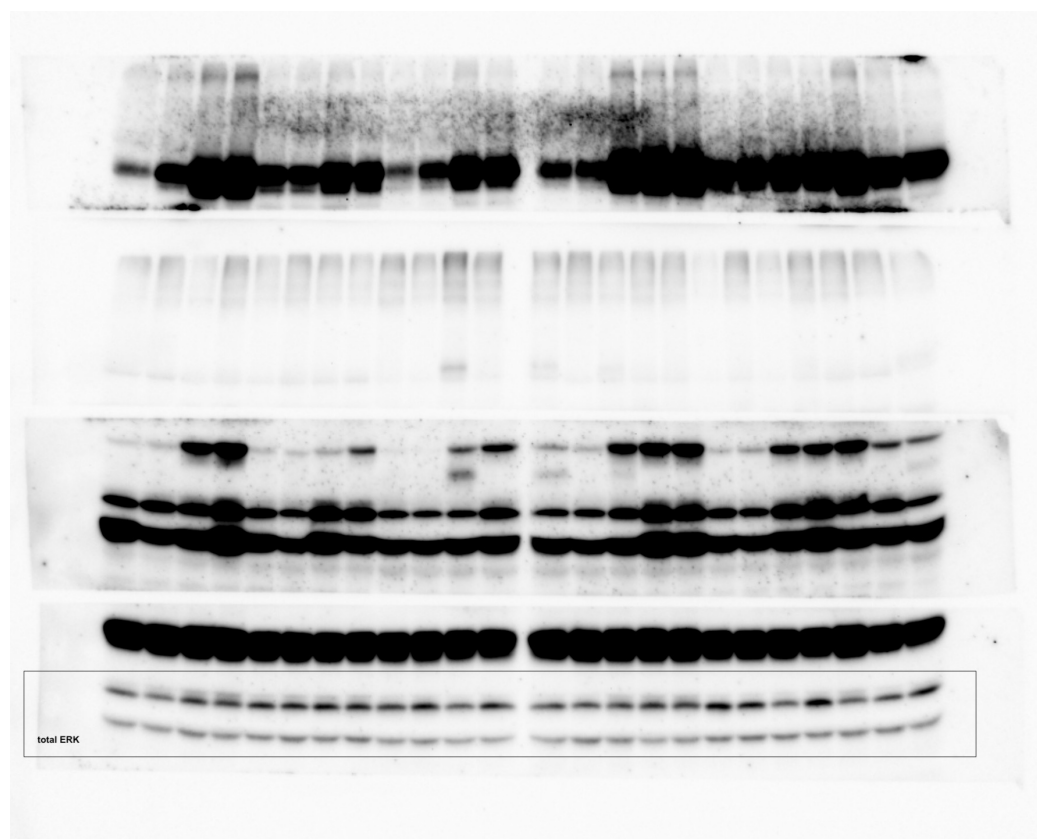


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Muscle pERK1/2

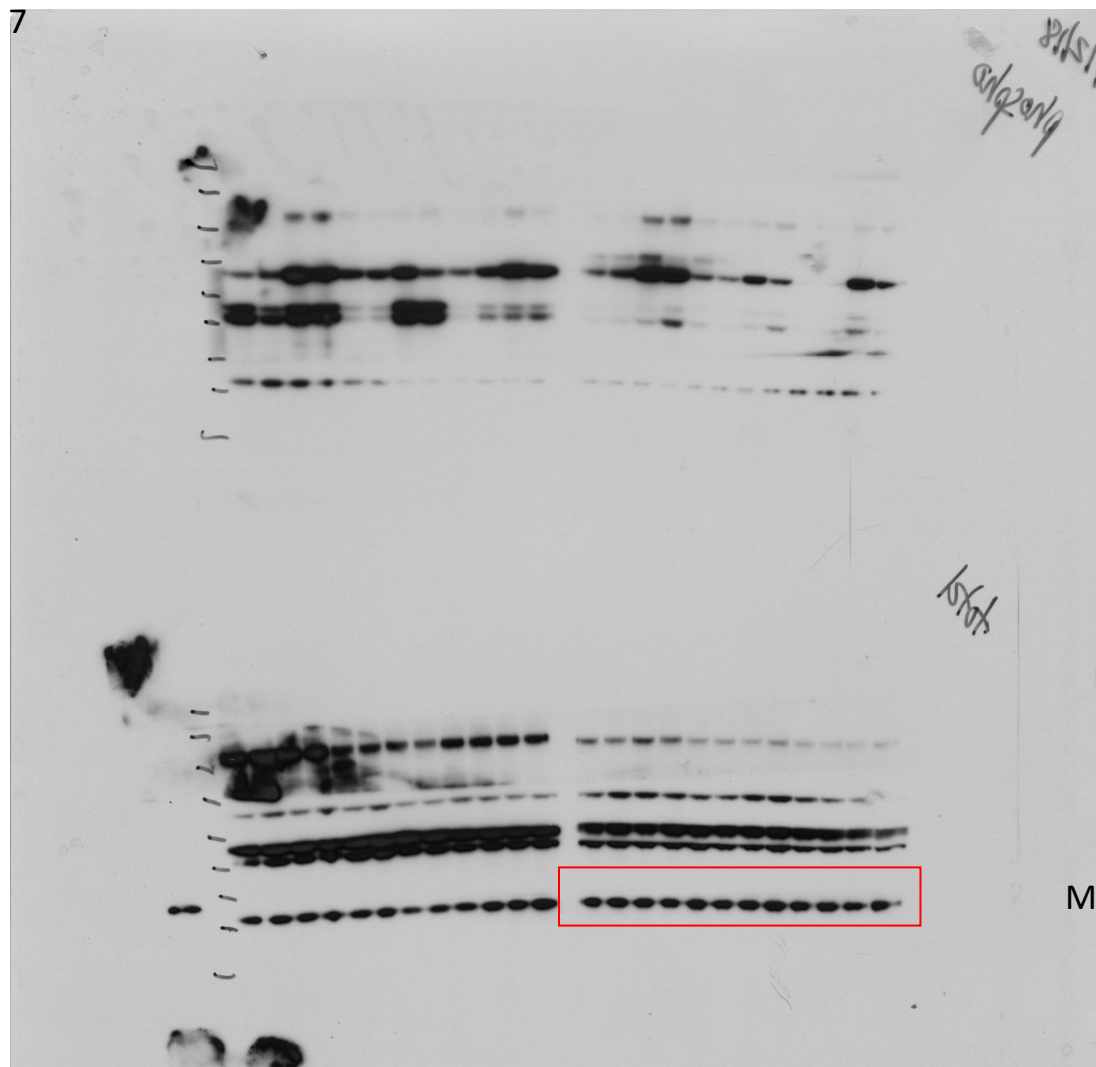


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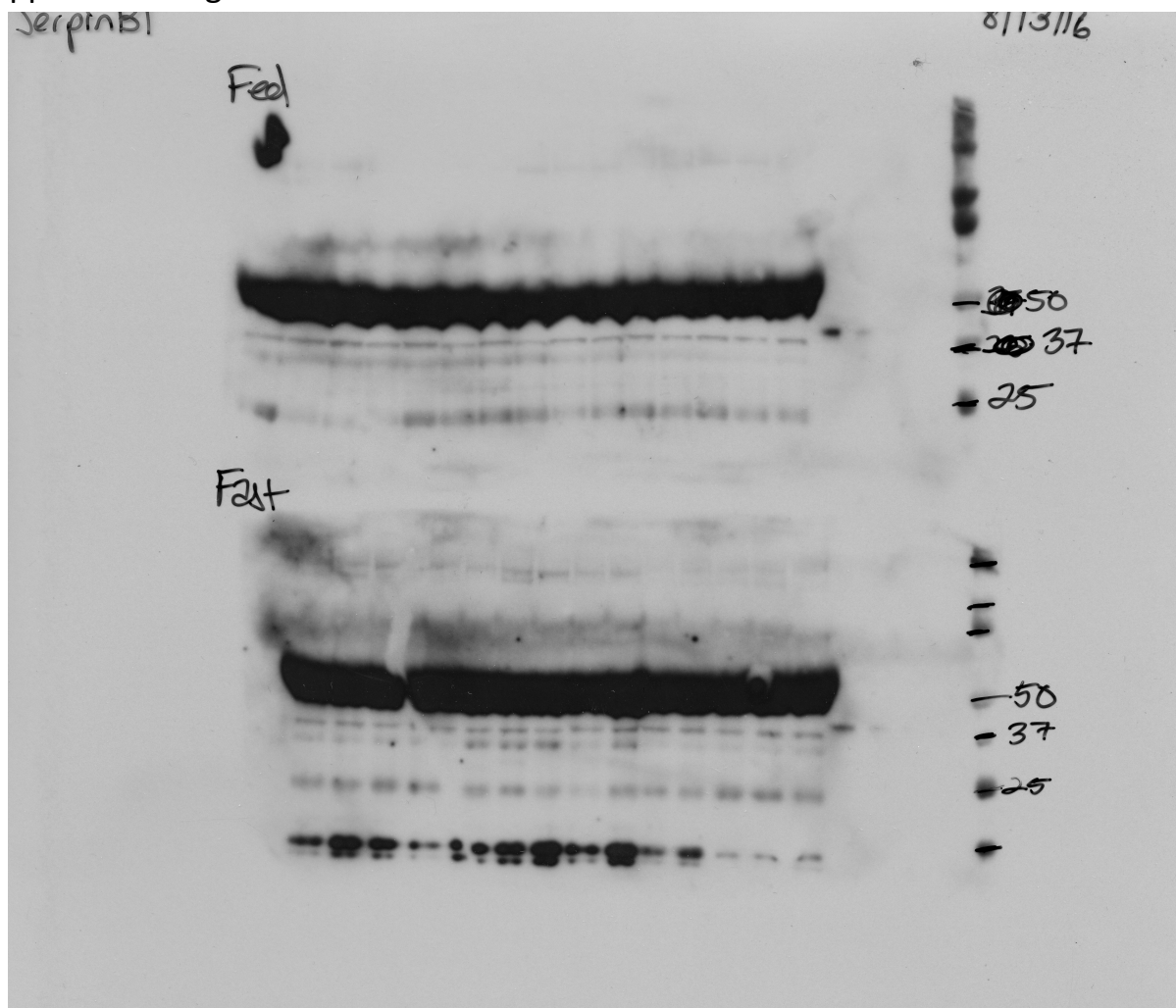
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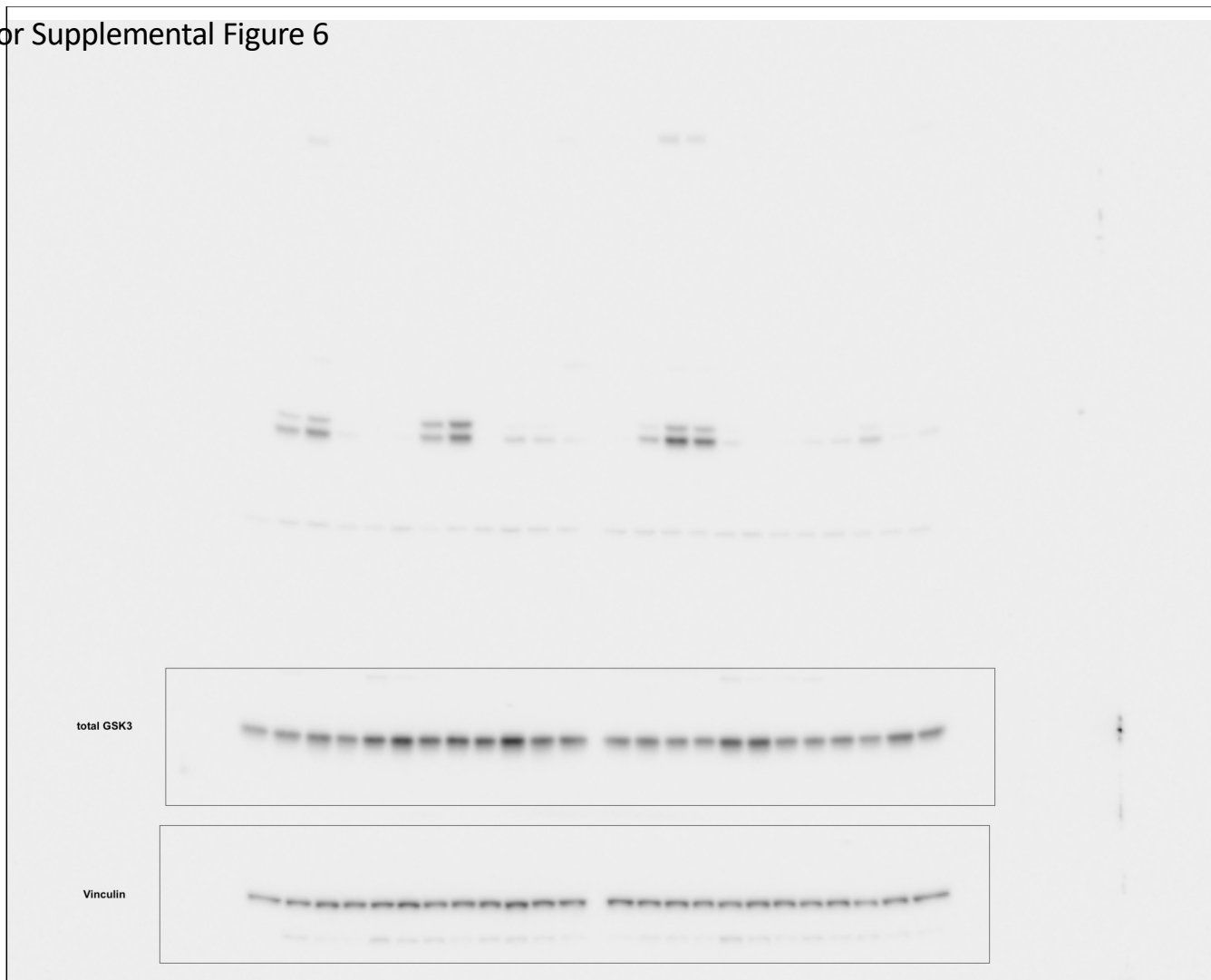


Muscle Grb2

Full unedited gel for Supplemental Figure 2



Full unedited gel for Supplemental Figure 6



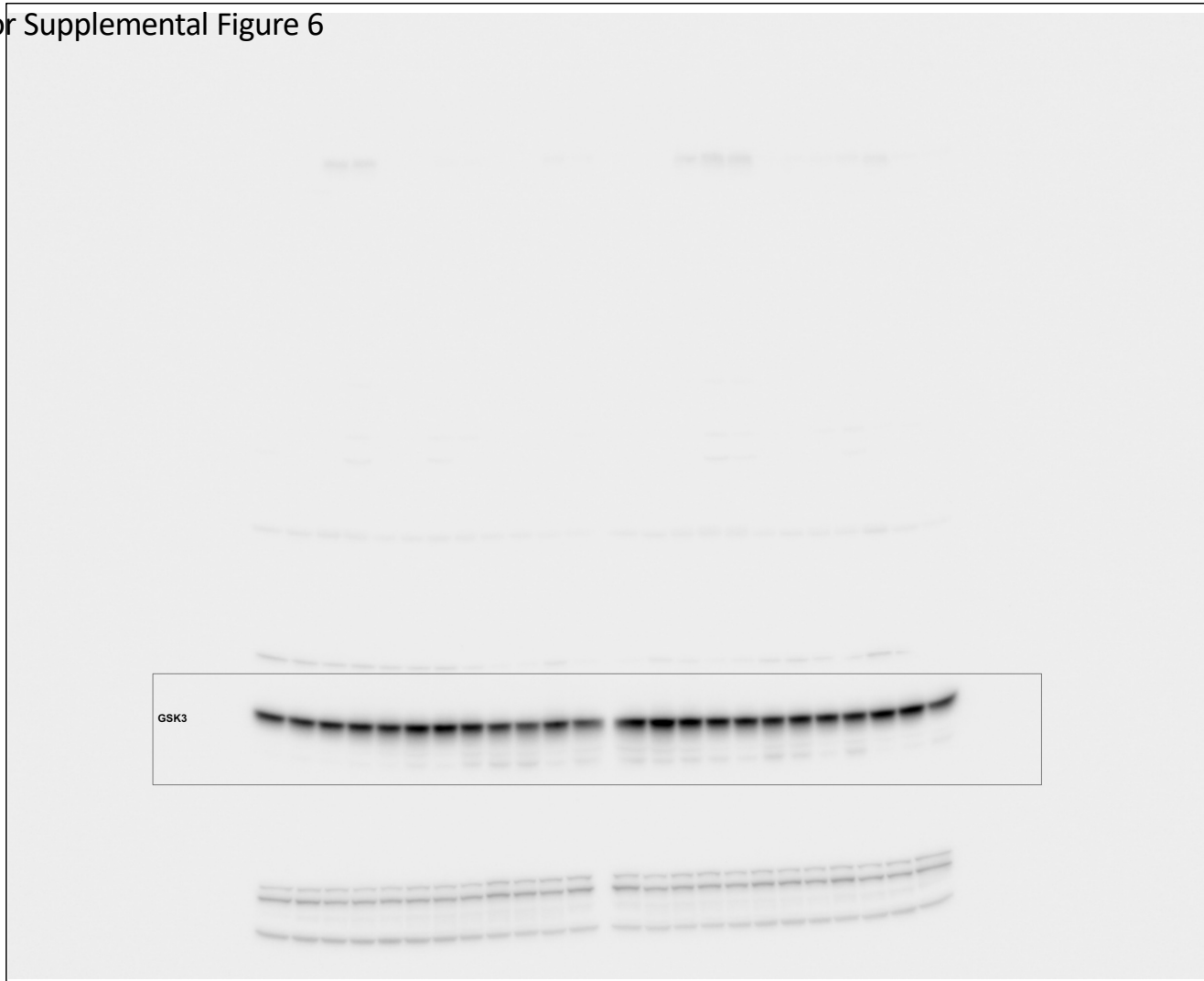
Liver total GSK3
and vinculin

total GSK3

Vinculin

Full unedited gel for Supplemental Figure 6

Muscle GSK3



Full unedited gel for Supplemental Figure 6

Muscle Vinculin

