S. Fig. 1. Body weight and pancreas weight of placental mTORKO\textsuperscript{pl} and TSC2KO\textsuperscript{pl} offspring and littermate controls. Body weights of adult (A) male mTORKO\textsuperscript{pl} and littermate controls (n=6-7), (A') male TSC2KO\textsuperscript{pl} and littermate controls (n=5-8), (B) female mTORKO\textsuperscript{pl} and littermate controls (n=11-16), and (B') female TSC2KO\textsuperscript{pl} and littermate controls (n=10-12). Pancreas weight normalized by body weight of adult (C) male mTORKO\textsuperscript{pl} and littermate controls (n=4), (C') male TSC2KO\textsuperscript{pl} and littermate controls (n=4-6), (D) female mTORKO\textsuperscript{pl} and littermate controls (n=9-14), and (D') female TSC2KO\textsuperscript{pl} and littermate controls (n=8-11). Liver weight normalized by body weight of adult (E) male mTORKO\textsuperscript{pl} and littermate controls (n=6-7) and (F) female mTORKO\textsuperscript{pl} and littermate controls (n=4). (G) Images of H&E staining performed on liver tissues from mTORKO\textsuperscript{pl} male and female offspring. Statistical analyses were conducted using an unpaired two-tailed t-test, with significance *p<0.05.
S. Fig. 2. Blood glucose and serum insulin levels of placental mTORKO_{pl} and TSC2KO_{pl} offspring and littermate controls. Non-fasting blood glucose of 90-day old (A) male mTORKO_{pl} and littermate controls (n=6-7), (A') male TSC2KO_{pl} and littermate controls (n=4-6), (B) female mTORKO_{pl} and littermate controls (n=11-16), and (B') female TSC2KO_{pl} and littermate controls (n=8-11). Non-fasting serum insulin of 90-day old (C) male mTORKO_{pl} and littermate controls (n=5-6), (C') male TSC2KO_{pl} and littermate controls (n=4), (D) female mTORKO_{pl} and littermate controls (n=5), and (D') female TSC2KO_{pl} and littermate controls (n=3). Fasting blood glucose of 90-day old (E) male mTORKO_{pl} and littermate controls (n=7-10), (E') male TSC2KO_{pl} and littermate controls (n=5-8), (F) female mTORKO_{pl} and littermate controls (n=11-16), and (F') female TSC2KO_{pl} and littermate controls (n=10-13). Fasting serum insulin of 90-day old (G) male mTORKO_{pl} and littermate controls (n=4-8), (G') male TSC2KO_{pl} and littermate controls (n=5), (H) female mTORKO_{pl} and littermate controls (n=5), and (H') female TSC2KO_{pl} and littermate controls (n=4). Statistical analyses were conducted using an unpaired two-tailed t-test with significance *p<0.05.
Figure S3

Adipose tissue

**mTOR Ctrl Saline** vs **mTOR Ctrl Insulin**

**mTOR KO Saline** vs **mTOR KO Insulin**

Adipose tissue

**TSC2 Ctrl Saline** vs **TSC2 Ctrl Insulin**

**TSC2 KO Saline** vs **TSC2 KO Insulin**

Skeletal muscle

**mTOR Ctrl Saline** vs **mTOR Ctrl Insulin**

**mTOR KO Saline** vs **mTOR KO Insulin**

Skeletal muscle

**TSC2 Ctrl Saline** vs **TSC2 Ctrl Insulin**

**TSC2 KO Saline** vs **TSC2 KO Insulin**

Skeletal muscle
S. Fig. 3. Insulin-Akt signaling in adipose tissue and skeletal muscle of placental mTORKO\textsuperscript{pl} and TSC2KO\textsuperscript{pl} adult offspring. (A) Representative Western blots of phosphorylated Akt at serine 473, total Akt, and vinculin from inguinal adipose tissue of 90-day-old mTOR control, mTORKO\textsuperscript{pl}, TSC2 control, and TSC2KO\textsuperscript{pl} male offspring injected with saline or 1 U/kg insulin. (B) Quantification of adipose tissue Western blots represented as fold-change relative to saline-treated mTOR control (n=4-6). (C) Quantification of adipose tissue Western blots represented as fold-change relative to saline-treated TSC2 control (n=3-4). (D) Representative Western blots of phosphorylated Akt at serine 473, total Akt, and vinculin from skeletal muscle of 90-day-old mTOR control, mTORKO\textsuperscript{pl}, TSC2 control, and TSC2KO\textsuperscript{pl} male offspring injected with saline or 1 U/kg insulin. (E) Quantification of skeletal muscle Western blots represented as fold-change relative to saline-treated mTOR control (n=3-6). (F) Quantification of skeletal muscle Western blots represented as fold-change relative to saline-treated TSC2 control (n=3-4). (G) Representative Western blots of phosphorylated Akt at serine 473, total Akt, and vinculin from inguinal adipose tissue of 90-day-old mTOR control, mTORKO\textsuperscript{pl}, TSC2 control, and TSC2KO\textsuperscript{pl} female offspring injected with saline or 1 U/kg insulin. (H) Quantification of adipose tissue Western blots represented as fold-change relative to saline-treated mTOR control (n=3-4). (I) Quantification of adipose tissue Western blots represented as fold-change relative to saline-treated TSC2 control (n=3-4). (J) Representative Western blots of phosphorylated Akt at serine 473, total Akt, and vinculin from skeletal muscle of 90-day-old mTOR control, mTORKO\textsuperscript{pl}, TSC2 control, and TSC2KO\textsuperscript{pl} female offspring injected with saline or 1 U/kg insulin. (K) Quantification of skeletal muscle Western blots represented as fold-change relative to saline-treated mTOR control (n=3). (L) Quantification of skeletal muscle Western blots represented as fold-change relative to saline-treated TSC2 control (n=3-4). Statistical analyses were conducted using one-way ANOVA with Tukey’s post-hoc test, with significance *p<0.05.
Figure S4

**Liver**
- mTOR Ctrl Saline
- mTOR Ctrl Insulin
- mTOR KO Saline
- mTOR KO Insulin

**Adipose tissue**
- mTOR Ctrl Saline
- mTOR Ctrl Insulin
- mTOR KO Saline
- mTOR KO Insulin

**Skeletal muscle**
- mTOR Ctrl Saline
- mTOR Ctrl Insulin
- mTOR KO Saline
- mTOR KO Insulin

**Liver**
- TSC2 Ctrl Saline
- TSC2 Ctrl Insulin
- TSC2 KO Saline
- TSC2 KO Insulin

**Adipose tissue**
- TSC2 Ctrl Saline
- TSC2 Ctrl Insulin
- TSC2 KO Saline
- TSC2 KO Insulin

**Skeletal muscle**
- TSC2 Ctrl Saline
- TSC2 Ctrl Insulin
- TSC2 KO Saline
- TSC2 KO Insulin
S. Fig. 4. Total Akt levels in liver, adipose, and skeletal muscle of placental mTORKO\textsuperscript{pl} and TSC2KO\textsuperscript{pl} offspring and littermate controls. Quantification of total Akt normalized to vinculin loading control in (A) liver, (A') adipose tissue, and (A'') skeletal muscle of male mTORKO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=3-6). Quantification of total Akt normalized to vinculin loading control in (B) liver, (B') adipose tissue, and (B'') skeletal muscle of male TSC2KO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=3-4). Quantification of total Akt normalized to vinculin loading control in (C) liver, (C') adipose tissue, and (C'') skeletal muscle of female mTORKO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=3-4). Quantification of total Akt normalized to vinculin loading control in (D) liver, (D') adipose tissue, and (D'') skeletal muscle of female TSC2KO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=3-5). Statistical analyses were conducted using one-way ANOVA with Tukey’s post-hoc test, with significance *p<0.05.
S. Fig. 5. Phospho-Akt levels normalized to vinculin in liver, adipose, and skeletal muscle of placental mTORKO<sup>pl</sup> and TSC2KO<sup>pl</sup> female offspring and littermate controls. Quantification of phospho-Akt normalized to vinculin loading control in (A) liver, (B) adipose tissue, and (C) skeletal muscle of female mTORKO<sup>pl</sup> and littermate controls with and without insulin stimulation (n=3-4). Quantification of phospho-Akt normalized to vinculin loading control in (D) liver, (E) adipose tissue, and (F) skeletal muscle of female TSC2KO<sup>pl</sup> and littermate controls with and without insulin stimulation (n=3-5). Statistical analyses were conducted using one-way ANOVA with Tukey’s post-hoc test, with significance *p<0.05, **p<0.01.
S. Fig. 6. Total hepatic S6 of placental mTORKO\textsuperscript{pl} and littermate controls. Quantification of total S6 normalized to vinculin loading control in liver of (A) male mTORKO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=5-7), and (B) female mTORKO\textsuperscript{pl} and littermate controls with and without insulin stimulation (n=3-4). Statistical analyses were conducted using one-way ANOVA with Tukey’s post-hoc test, with significance *p<0.05.
S. Fig. 7. Validation of RNA sequencing candidates. Hepatic (A) Cxcl1 mRNA expression in TSC2KO\textsuperscript{pl} males compared to littermate controls (n=3-4), and (B) Slc41a2 mRNA expression in mTORKO\textsuperscript{pl} females compared to littermate controls (n=3-4). Statistical analyses were conducted using a Student’s t-test, with significance *p<0.05.
Male liver: $\text{mTORKO}^{pl}$ versus $\text{TSC2KO}^{pl}$

S. Fig. 8. RNA sequencing comparisons of male $\text{mTORKO}^{pl}$ and $\text{TSC2KO}^{pl}$ male offspring. Fold-change>2 and FDR<0.05. Red indicates increased expression. Blue indicates decreased expression.
S. Fig. 9. RNA sequencing comparisons of female mTORKO^{pl} and TSC2KO^{pl} male offspring. Fold-change>2 and FDR<0.05. Red indicates increased expression. Blue indicates decreased expression.

**Female liver: mTORKO^{pl} versus TSC2KO^{pl}**

Fold-change>2 and FDR<0.05. Red indicates increased expression. Blue indicates decreased expression.
Figure S10

A

NCD

Serum Mup1 (ng/mL)

mTOR Ctrl M
mTOR KO M
TSC2 Ctrl M
TSC2 KO M

B

Female

mTOR
TSC2
C  C
KO  KO

Male

mTOR
TSC2
C  C
KO  KO

MUP 20 kDa
Vinculin 124 kDa

C

D

E

F

G

H

I

J

K

MUP/vinculin (Fold-change)

mTOR Ctrl F
mTORKO F
TSC2 Ctrl F
TSC2KO F

mTOR Ctrl M
mTORKO M
TSC2 Ctrl M
TSC2KO M

mTOR Fasting_Females
mTOR Fasting_Males

TSC2 Fasting_Females
TSC2 Fasting_Males

MUP/vinculin (Fold-change)

mTOR Ctrl
mTOR KO
TSC2 Ctrl
TSC2 KO

Serum Mup1 (ng/mL)

mTOR Fasting_Females
mTOR Fasting_Males

MUP/vinculin (Fold-change)

mTOR Ctrl
mTOR KO
TSC2 Ctrl
TSC2 KO

MUP protein expression
Fasted liver_mTOR females

MUP/vinculin (Fold-change)

mTOR Ctrl Saline
mTOR Ctrl Insulin
mTOR KO Saline
mTOR KO Insulin

Serum Mup1 (ng/mL)
S. Fig. 10. Comparing serum and hepatic protein levels of Mup1 between males and females, in fasting state, and in response to insulin. (A) Circulating Mup1 levels in female (right) and male (left) mTORKO\textsuperscript{pl} and TSC2KO\textsuperscript{pl} offspring and littermate controls. (B) Representative Western blots of MUP and vinculin from livers of 90-day-old female and male offspring; mTORKO\textsuperscript{pl} and littermate control females quantified in (C, n=5-7), TSC2KO\textsuperscript{pl} and littermate control females quantified in (D, n=4-5), mTORKO\textsuperscript{pl} and littermate control males quantified in (E, n=3), and TSC2KO\textsuperscript{pl} and littermate control males quantified in (F, n=3). Western blot quantification represented as fold-change relative to littermate controls. Fasting serum levels of Mup1 in (G) mTORKO\textsuperscript{pl} and littermate control females (n=5), (H) TSC2KO\textsuperscript{pl} and littermate control females (n=5), (I) mTORKO\textsuperscript{pl} and littermate control males (n=5-6), and (J) TSC2KO\textsuperscript{pl} and littermate control males (n=4). (K) Quantification of Western blot measuring hepatic MUP expression in mTORKO\textsuperscript{pl} females and littermate controls treated with 1U/kg insulin or control-treated with saline. Statistical analyses were conducted using an unpaired two-tailed t-test or a one-way ANOVA with Tukey’s post-hoc test, with significance *p<0.05, **p<0.01, ***p<0.001.
Supplementary Table 1: Gene ontology and IPA results

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Supplementary Table 2: RT-qPCR primer sequences

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