

**Figure S1. (A)** Map of the plasmid harboring the "CAG-loxp-bgal-stop-loxp-IR" cassette for pronuclear injection. **(B)** IR mRNA expression measured by qPCR in heart from control and IRMOE mice (n=5). **(C)** Western blot showing IR protein level in heart from control and IRMOE mice (n=5). Data represent mean  $\pm$  SD, Student's *t*-test.



**Figure S2.** (A)  $O_2$  consumption rate, (B)  $CO_2$  production rate, (C) Activity and (D) Respiration exchange ratio in control and IRMOE mice on chow diet (n=5). Data represent mean <u>+</u> SEM, \*p<0.05.



**Figure S3.(A)** Glucose tolerance test in 2.5 months old control and IRMOE mice on chow diet (n=5). **(B)** Plasma insulin levels in 5-month-old Ctl and IRMOE mice on chow diet (n = 5). **(C)** Insulin tolerance tests in 5-month-old Ctl and IRMOE mice on chow diet (n = 5). **(D)** Representative Insulin staining of pancreas paraffin section in 3.5 months old Ctl and IRMOE mice on chow diet (n=3), scale bar = 100 $\mu$ m. Data represent mean <u>+</u> SD.



**Figure S4.** Glucose uptake in **(A)** Gastrocnemius **(B)** Quadriceps **(C)** EDL **(D)** Soleus muscles and **(E)** Epididymal white fat **(F)** Subcutaneous white fat **(G)** Brain and **(H)** Brown fat in 7 months old male mice measured after euglycemic-hyperinsulinemic clamps (n=8). **(I)** Western blot showing insulin signaling in tibialis anterior muscles under basal conditions and after vena cava injection of insulin (n = 3). **(J)** Gluconeogenic gene expression in liver measured by qPCR in fed and fasted control and IRMOE mice (n=5-7). **(K)** Plasma amino acids levels in control and IRMOE mice after overnight fast (n=8-11). Data represent mean<u>+</u>SD, \*p<0.05.



## **IRMOE vs. Ctl downregulated**

(21)

REACTOME PRE NOTCH TRANSCRIPTION AND TRANSLATION -

REACTOME NOTCH HLH TRANSCRIPTION PATHWAY-

REACTOME PRE NOTCH EXPRESSION AND PROCESSING -	(36)
BIOCARTA PTC1 PATHWAY -	(7)
PID E2F PATHWAY -	(55)
BIOCARTA ETS PATHWAY -	(17)
BIOCARTA CTCF PATHWAY	(19)
REACTOME HYALURONAN METABOLISM -	(12)
REACTOME TRAF6 MEDIATED IRF7 ACTIVATION -	(17)
BIOCARTA VDR PATHWAY -	(12)
KEGG BASAL TRANSCRIPTION FACTORS -	(30)
PID IL27 PATHWAY -	(11)
KEGG NOTCH SIGNALING PATHWAY -	(42)
ST IL 13 PATHWAY -	(4)
BIOCARTA MCM PATHWAY	(15)
PID MYC REPRESS PATHWAY -	(54)
BIOCARTA EPONFKB PATHWAY -	(8)
REACTOME MEIOTIC SYNAPSIS -	(26)
REACTOME INTERFERON SIGNALING -	(110)
ST WNT BETA CATENIN PATHWAY -	(29)
BIOCARTA LONGEVITY PATHWAY -	(14)
PID ATR PATHWAY -	(29)
PID HNF3A PATHWAY-	(25)
KEGG TGF BETA SIGNALING PATHWAY -	(67)
REACTOME METABOLISM OF POLYAMINES -	(13)
	-log10P value

(12)

Figure S5. Top ranked pathways (A) up-regulated and (B) down-regulated in quadriceps muscle in IRMOE mice compared to control

S5B



**Figure S6.** (A)  $CO_2$  production rate and (B) activity in control and IRMOE mice after 11 weeks on HFD (n=5-6). (C) Q-PCR of quadriceps muscles from 24hr fasted chow fed control and IRMOE mice (n=5-6). Data represent mean <u>+</u> SD, \*p<0.05.