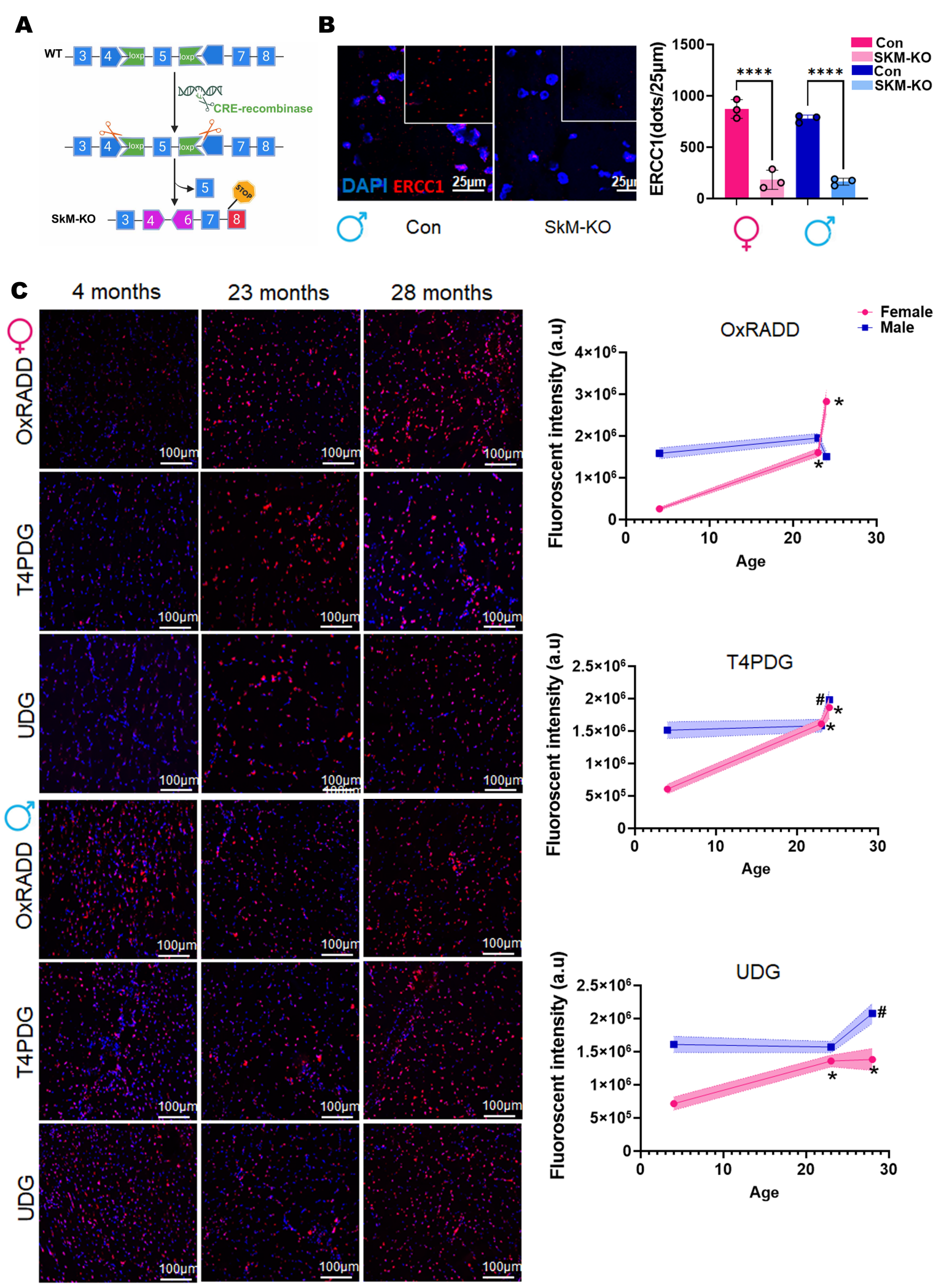
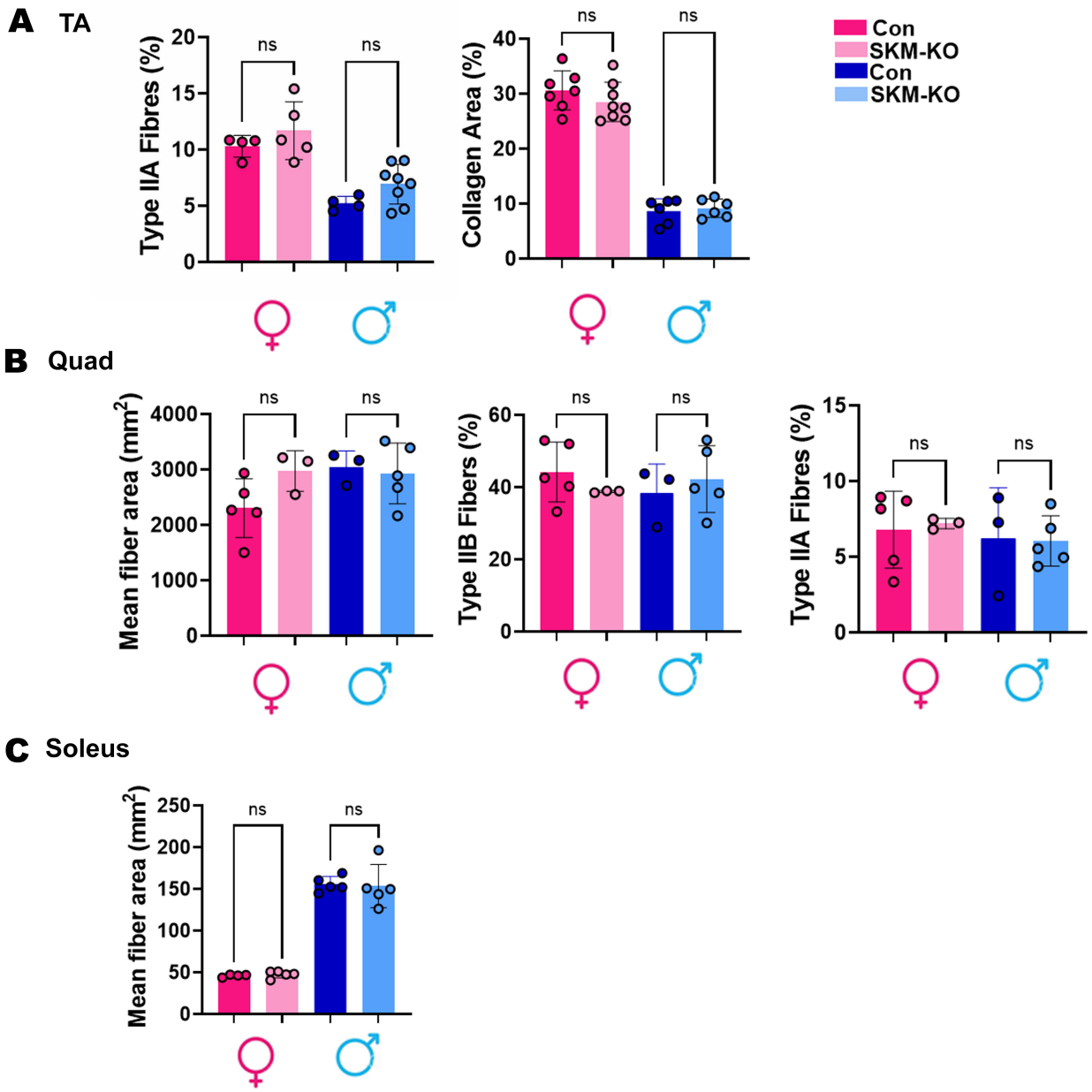
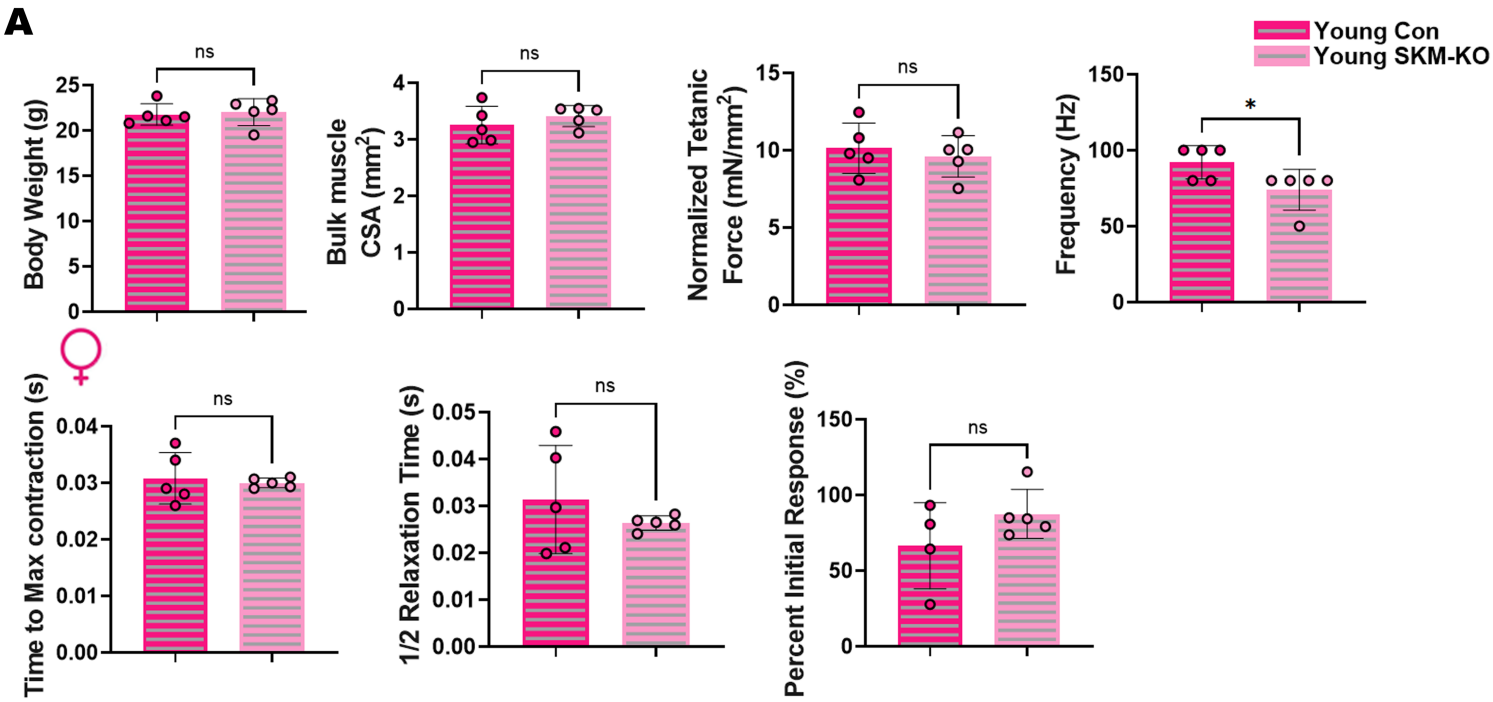

A
WT
loxp
CRE-recombinase
SkM-KO
STOP
B
DAPI ERCC1
25μm
Con
SkM-KO
ERCC1(dots/25μm)
****
Con
SKM-KO
C
4 months
23 months
28 months
OxRADD
T4PDG
UDG
100μm
Female
Male
Fluorescent intensity (a.u)
Age
#
*

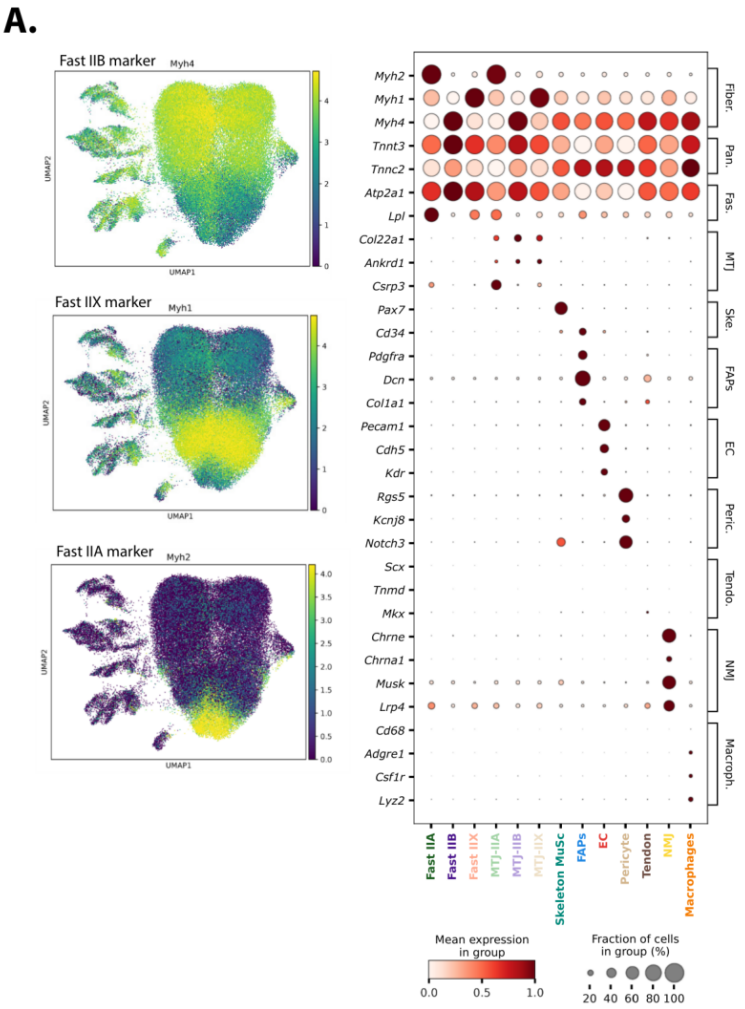
Supp Fig 1

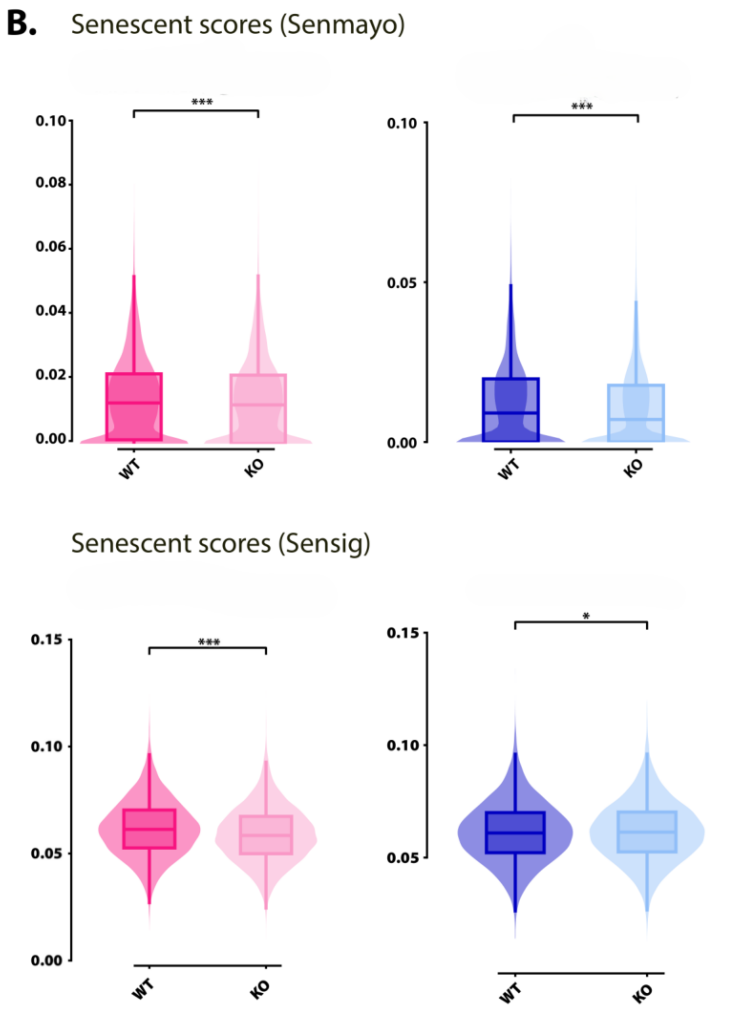

A
TA
Type IIA Fibres (%)
Collagen Area (%)
ns
Con
SKM-KO
Con
SKM-KO
B
Quad
Mean fiber area (mm²)
Type IIB Fibers (%)
Type IIA Fibres (%)
C
Soleus
Mean fiber area (mm²)

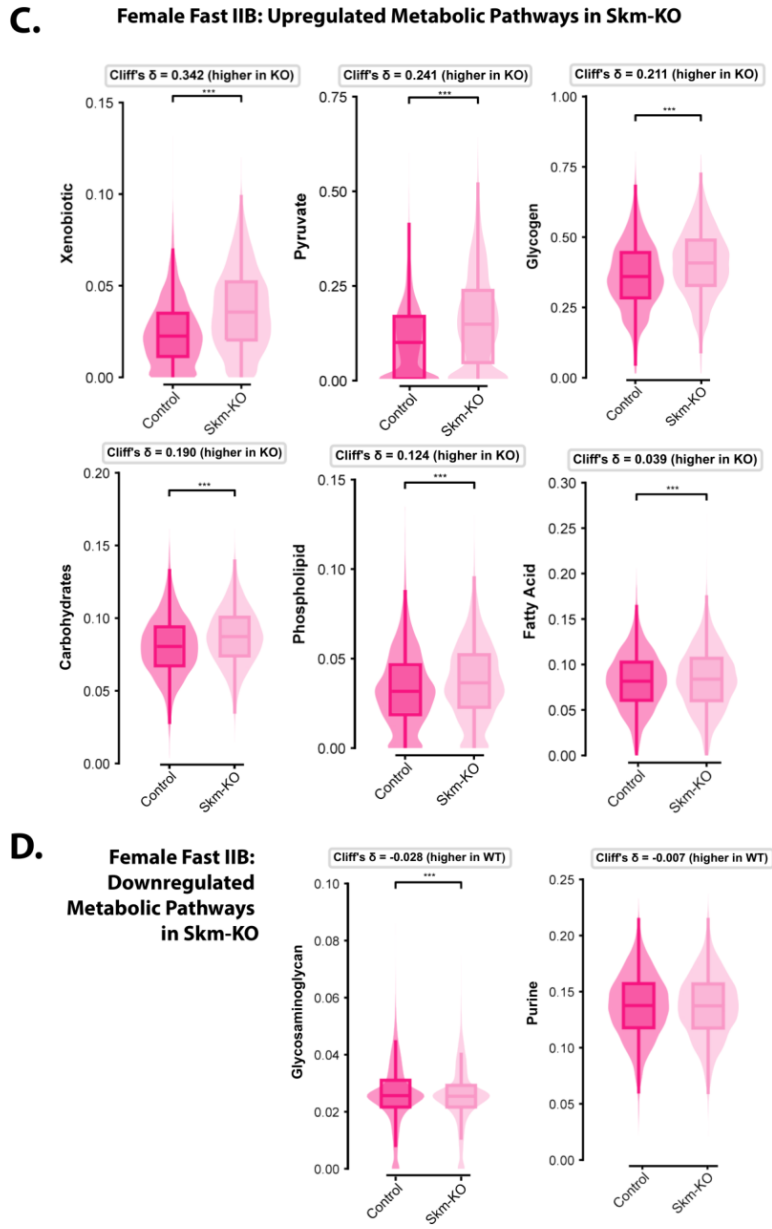
Supp Fig 2


A
Young Con
Young SKM-KO
Body Weight (g)
ns
Bulk muscle CSA (mm²)
ns
Normalized Tetanic Force (mN/mm²)
ns
Frequency (Hz)
*
♀
Time to Max contraction (s)
ns
1/2 Relaxation Time (s)
ns
Percent Initial Response (%)
ns

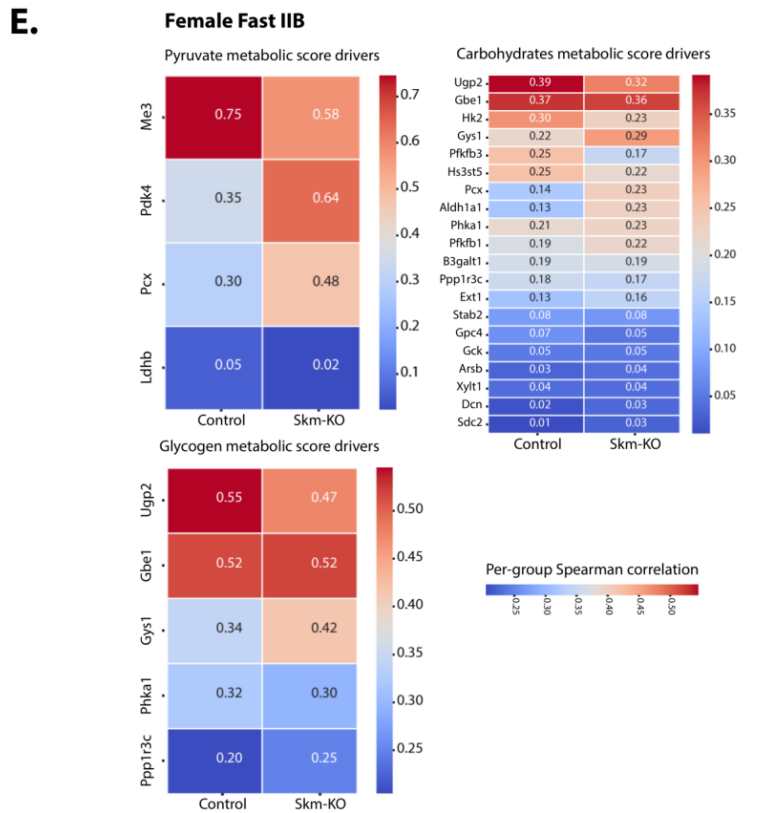
Supp fig 3


A.
Fast IIB marker Myh4
Fast IIX marker Myh1
Fast IIA marker Myh2
UMAP1
UMAP2
Myh2
Myh1
Myh4
Tnnt3
Tnnc2
Atp2a1
Lpl
Col22a1
Ankrd1
Csrp3
Pax7
Cd34
Pdgfra
Dcn
Col1a1
Pecam1
Cdh5
Kdr
Rgs5
Kcnj8
Notch3
Scx
Tnmd
Mkx
Chrne
Chrna1
Musk
Lrp4
Cd68
Adgre1
Csf1r
Lyz2
Fiber.
Pan.
Fas.
MTJ
Ske.
FAPs
EC
Peric.
Tendo.
NMJ
Macroph.
Fast IIA
Fast IIB
Fast IIX
MTJ-IIA
MTJ-IIB
MTJ-IIX
Skeleton MuSc
FAPs
EC
Pericyte
Tendon
NMJ
Macrophages
Mean expression in group
0.0
0.5
1.0
Fraction of cells in group (%)
20 40 60 80 100


B.
Senescent scores (Senmayo)
Senescent scores (Sensig)
***
*
WT
KO

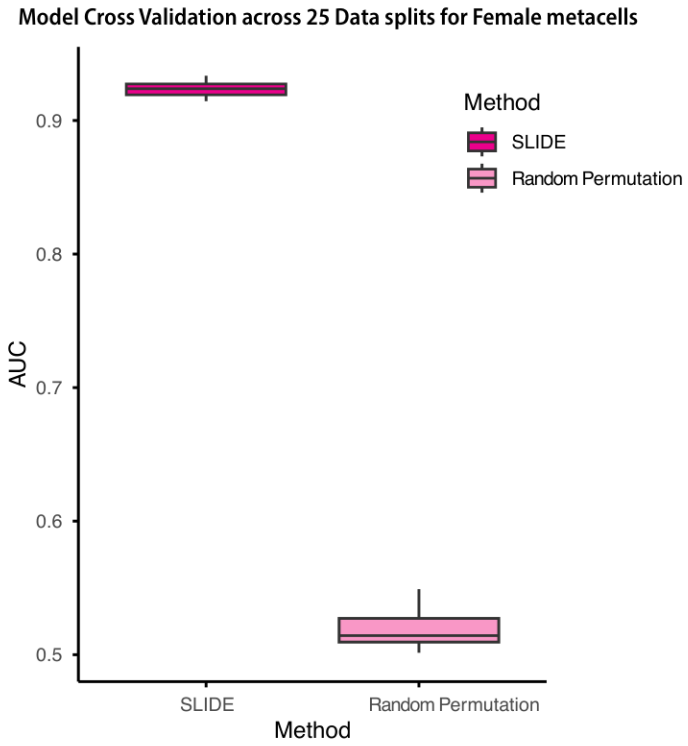

C.
Female Fast IIB: Upregulated Metabolic Pathways in Skm-KO
Cliff's δ = 0.342 (higher in KO)
Cliff's δ = 0.241 (higher in KO)
Cliff's δ = 0.211 (higher in KO)
Cliff's δ = 0.190 (higher in KO)
Cliff's δ = 0.124 (higher in KO)
Cliff's δ = 0.039 (higher in KO)
Xenobiotic
Pyruvate
Glycogen
Carbohydrates
Phospholipid
Fatty Acid
Control
Skm-KO

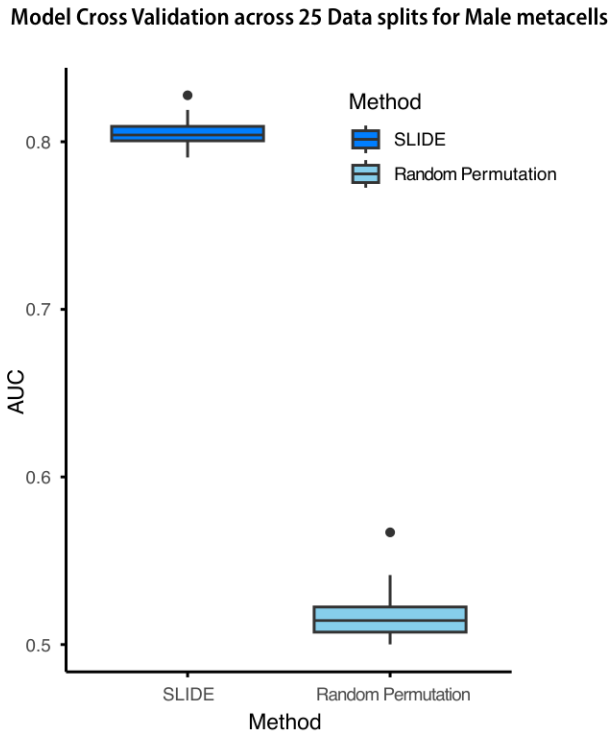
D.
Female Fast IIB: Downregulated Metabolic Pathways in Skm-KO
Cliff's δ = -0.028 (higher in WT)
Cliff's δ = -0.007 (higher in WT)
Glycosaminoglycan
Purine
Control
Skm-KO


E.
Female Fast IIB
Pyruvate metabolic score drivers
Me3
Pdk4
Pcx
Ldhb
0.75
0.58
0.35
0.64
0.30
0.48
0.05
0.02
Control
Skm-KO
Carbohydrates metabolic score drivers
Ugp2 0.39 0.32
Gbe1 0.37 0.36
Hk2 0.30 0.23
Gys1 0.22 0.29
Pfkfb3 0.25 0.17
Hs3st5 0.25 0.22
Pcx 0.14 0.23
Aldh1a1 0.13 0.23
Phka1 0.21 0.23
Pfkfb1 0.19 0.22
B3galt1 0.19 0.19
Ppp1r3c 0.18 0.17
Ext1 0.13 0.16
Stab2 0.08 0.08
Gpc4 0.07 0.05
Gck 0.05 0.05
Arsb 0.03 0.04
Xylt1 0.04 0.04
Dcn 0.02 0.03
Sdc2 0.01 0.03
Glycogen metabolic score drivers
Ugp2
Gbe1
Gys1
Phka1
Ppp1r3c
0.55
0.47
0.52
0.52
0.34
0.42
0.32
0.30
0.20
0.25
Per-group Spearman correlation

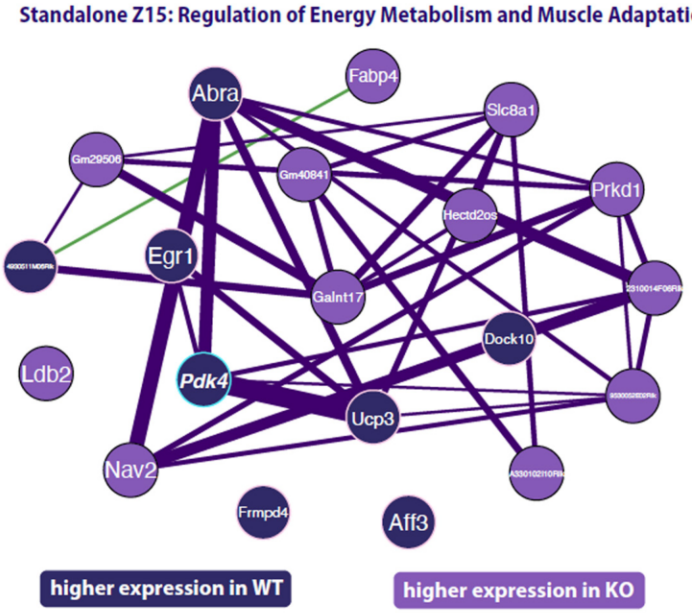
Supp Fig 4

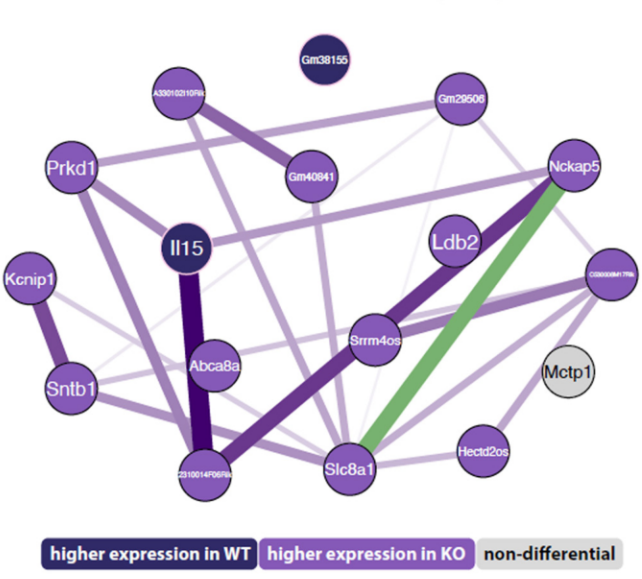
A.


Model Cross Validation across 25 Data splits for Female metacells
Method
SLIDE
Random Permutation
AUC
0.9
0.8
0.7
0.6
0.5
SLIDE
Random Permutation
Method

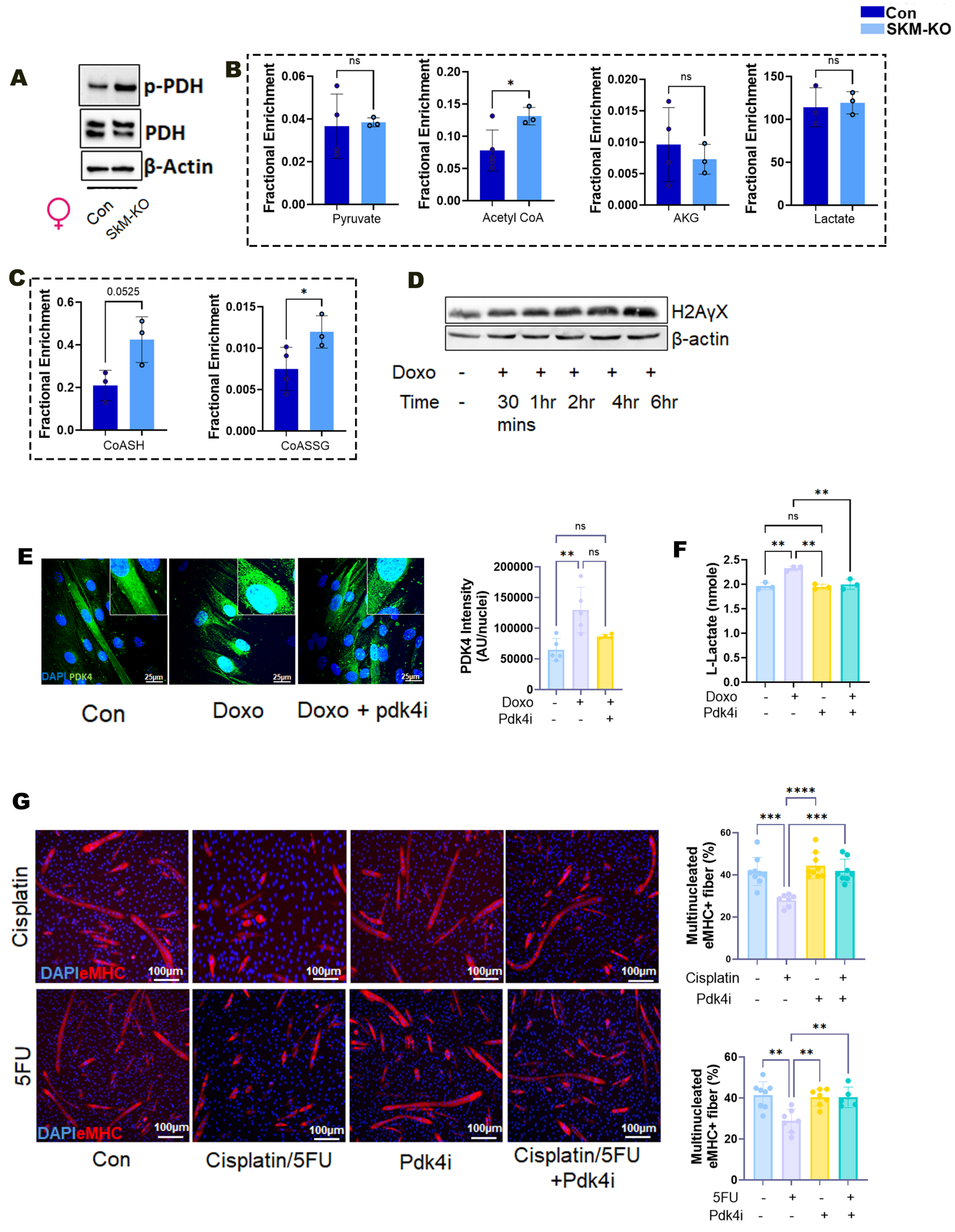

Model Cross Validation across 25 Data splits for Male metacells
Method
SLIDE
Random Permutation
AUC
0.8
0.7
0.6
0.5
SLIDE
Random Permutation
Method

B.

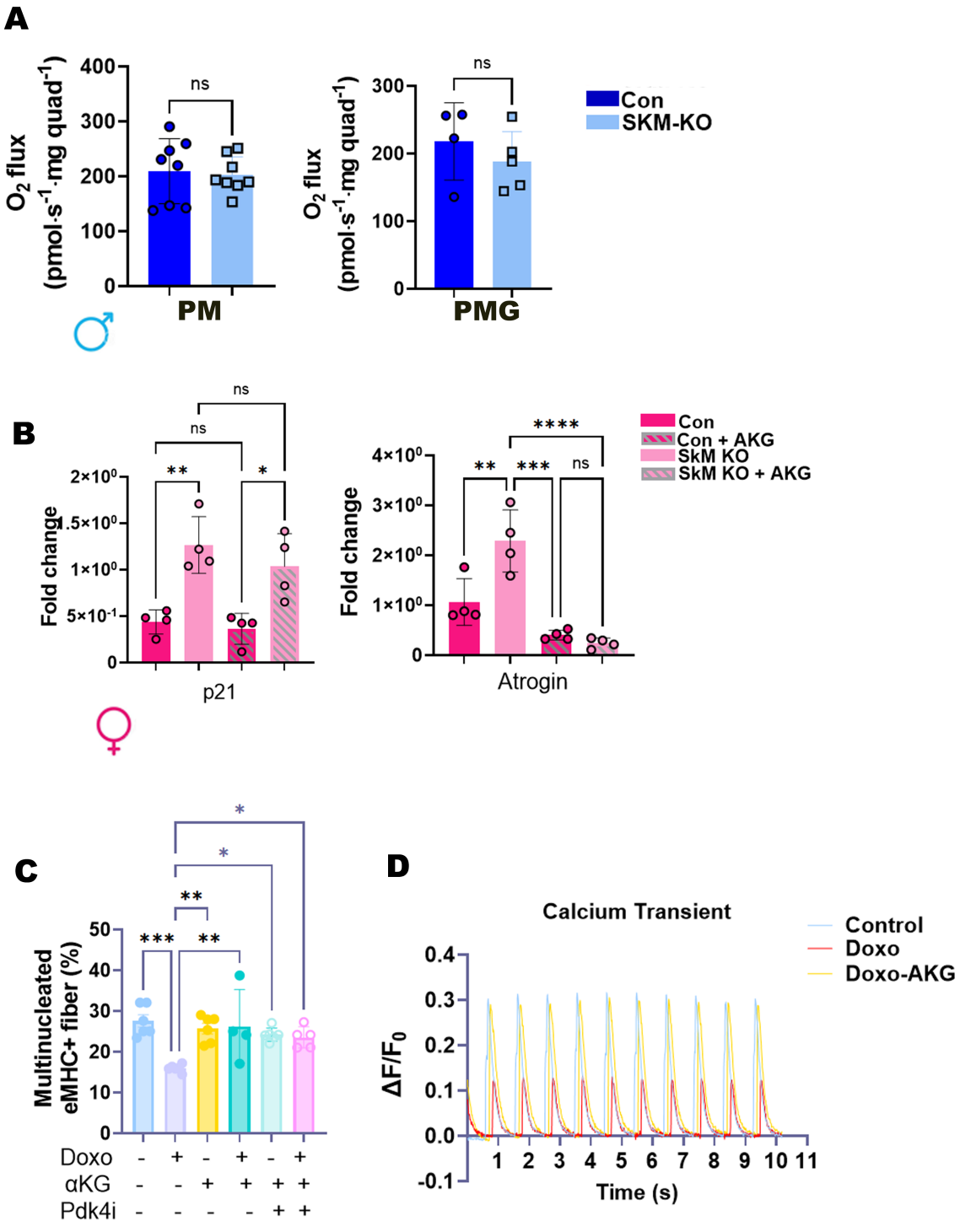

Standalone Z15: Regulation of Energy Metabolism and Muscle Adaptation
Abra
Fabp4
Slc8a1
Gm29506
Gm40841
Prkd1
Hectd2os
Egr1
Galnt17
Dock10
Ldb2
Pdk4
Ucp3
Nav2
Frmpd4
Aff3
higher expression in WT
higher expression in KO


Standalone Z29: Calcium Signaling
Gm38155
Gm29506
Prkd1
Gm40841
Nckap5
Il15
Ldb2
Kcnip1
Srrm4os
Abca8a
Mctp1
Sntb1
Hectd2os
Slc8a1
higher expression in WT
higher expression in KO
non-differential

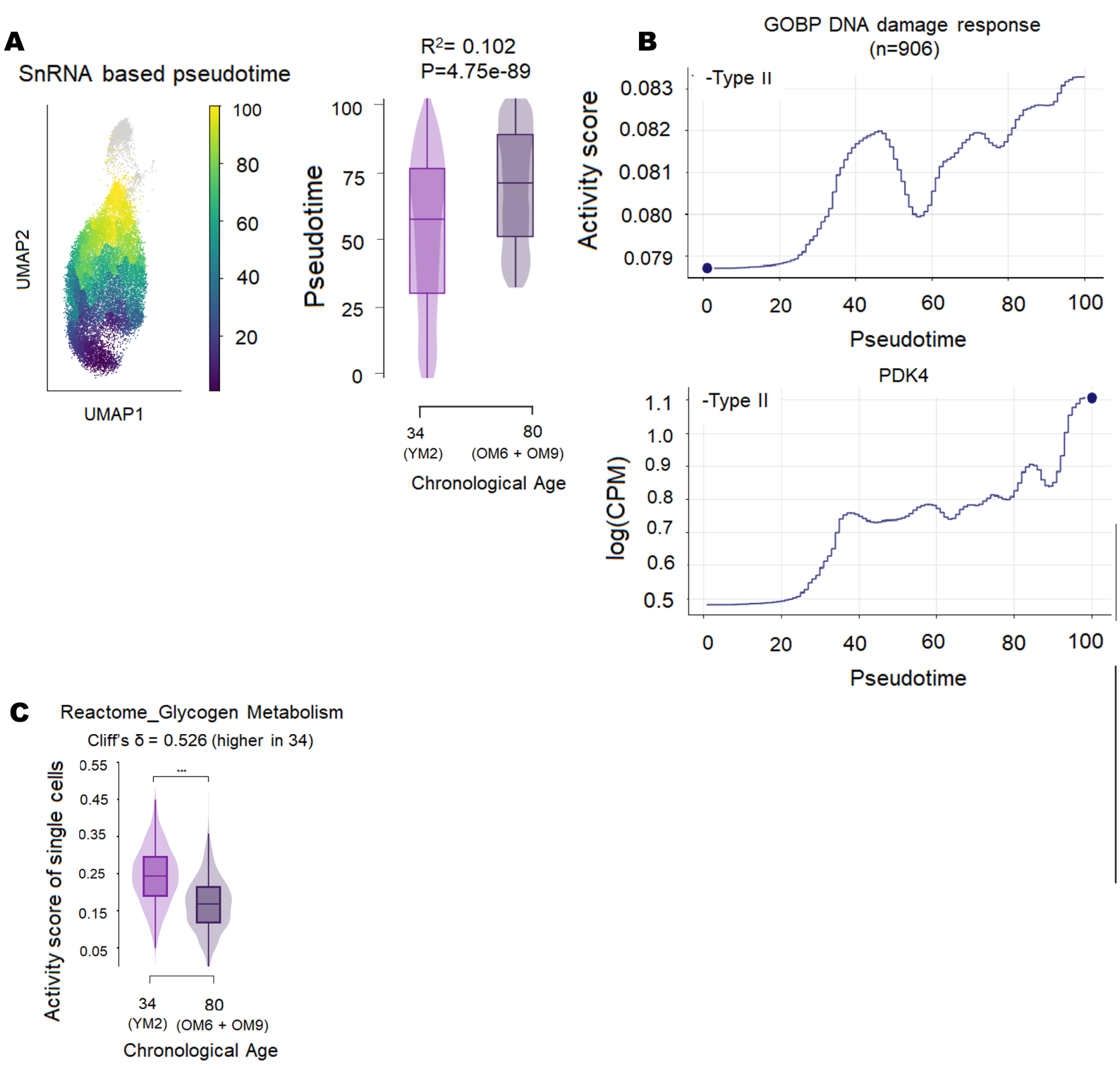
Supp fig 5


Con
SKM-KO
A
p-PDH
PDH
β-Actin
Con
SkM-KO
B
Fractional Enrichment
Pyruvate
Acetyl CoA
AKG
Lactate
ns
*
C
0.0525
CoASH
CoASSG
D
H2AγX
β-actin
Doxo - + + + + +
Time - 30 mins 1hr 2hr 4hr 6hr
E
DAPI PDK4
25μm
Con
Doxo
Doxo + pdk4i
PDK4 Intensity (AU/nuclei)
Doxo - + +
Pdk4i - - +
F
L-Lactate (nmole)
Doxo - + - +
Pdk4i - - + +
G
Cisplatin
5FU
DAPI eMHC
100μm
Con
Cisplatin/5FU
Pdk4i
Cisplatin/5FU +Pdk4i
Multinucleated eMHC+ fiber (%)
Cisplatin - + - +
Pdk4i - - + +
5FU - + - +
Pdk4i - - + +

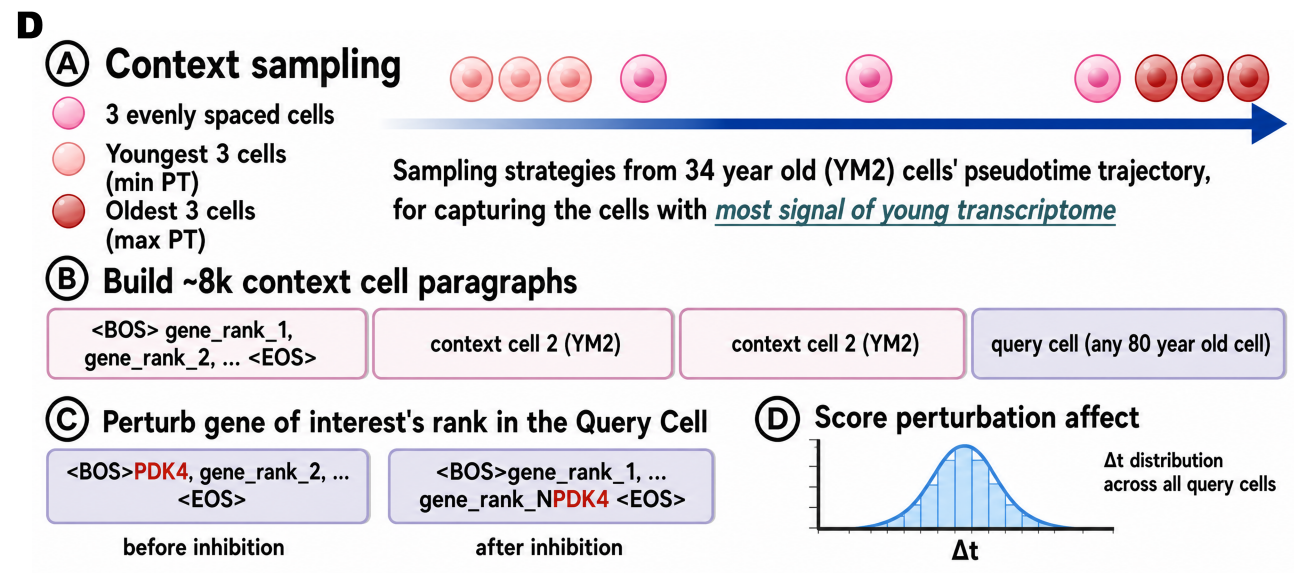
Supp fig 6


A
O_2 flux (pmol·s^{-1}·mg quad^{-1})
ns
PM
PMG
Con
SKM-KO
B
Fold change
p21
Atrogin
Con
Con + AKG
SkM KO
SkM KO + AKG
C
Multinucleated eMHC+ fiber (%)
Doxo
αKG
Pdk4i
D
Calcium Transient
Control
Doxo
Doxo-AKG
ΔF/F$_0$
Time (s)

Supp fig 7


A
SnRNA based pseudotime
UMAP2
UMAP1
100
80
60
40
20
R2= 0.102
P=4.75e-89
Pseudotime
100
75
50
25
0
34
(YM2)
80
(OM6 + OM9)
Chronological Age
B
GOBP DNA damage response
(n=906)
-Type II
Activity score
0.083
0.082
0.081
0.080
0.079
0
20
40
60
80
100
Pseudotime
PDK4
-Type II
log(CPM)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0
20
40
60
80
100
Pseudotime

C
Reactome_Glycogen Metabolism
Cliff's δ = 0.526 (higher in 34)
***
Activity score of single cells
0.55
0.45
0.35
0.25
0.15
0.05
34
(YM2)
80
(OM6 + OM9)
Chronological Age


D
A Context sampling
3 evenly spaced cells
Youngest 3 cells
(min PT)
Oldest 3 cells
(max PT)
Sampling strategies from 34 year old (YM2) cells' pseudotime trajectory,
for capturing the cells with most signal of young transcriptome
B Build ~8k context cell paragraphs
<BOS> gene_rank_1,
gene_rank_2, ... <EOS>
context cell 2 (YM2)
context cell 2 (YM2)
query cell (any 80 year old cell)
C Perturb gene of interest's rank in the Query Cell
<BOS>PDK4, gene_rank_2, ...
<EOS>
before inhibition
<BOS>gene_rank_1, ...
gene_rank_NPDK4 <EOS>
after inhibition
D Score perturbation affect
Δt distribution
across all query cells
Δt