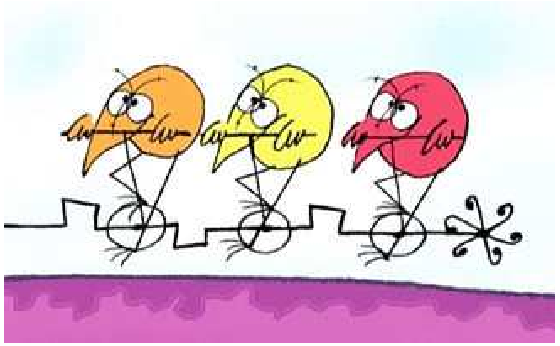
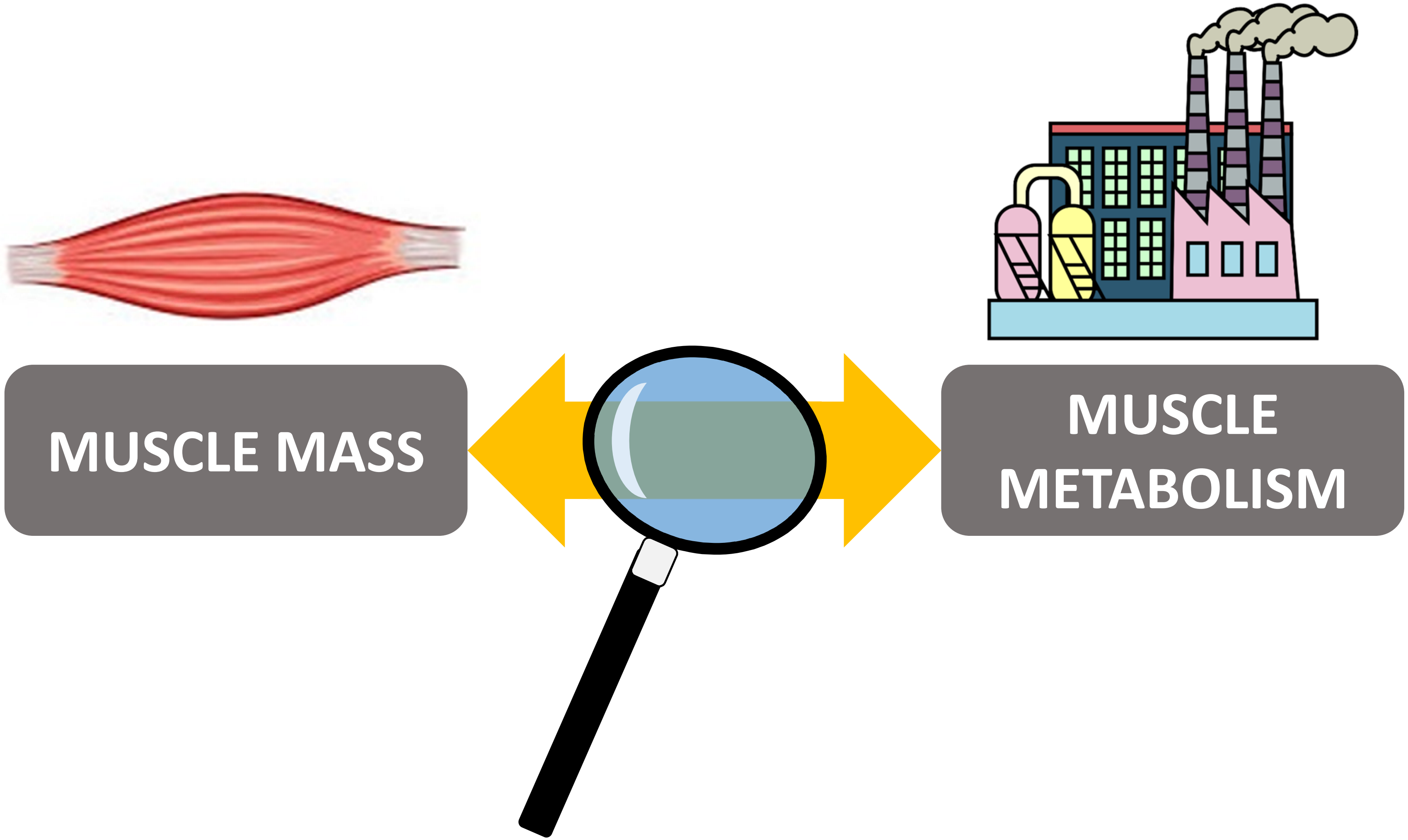
How muscle stops building when it's working?



F. FAVIER

UMR INRA 866 DMEM, Université Montpellier


MUSCLE MASS
MUSCLE METABOLISM

Muscle composition

Myofibrils (proteins) ≈80%

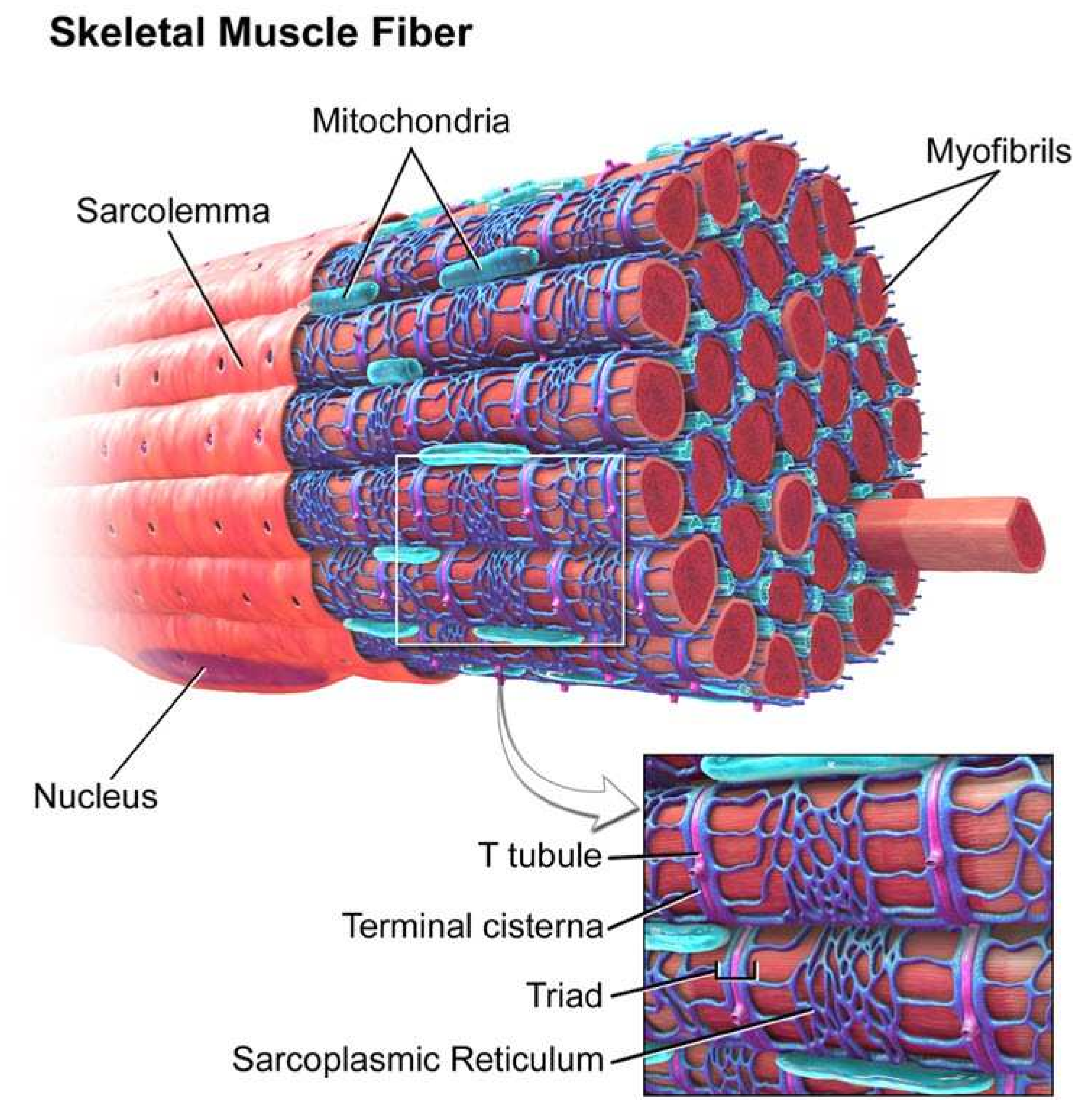
Mitochondria (proteins/p-lipids/DNA**) ≈5%**

SR+TT (proteins/Ca^{2+}/p-lipids**) ≈3-4%**

Glycogen ≈3%

Nuclei (nucleic acids/proteins**) ≈3% ?**

Lipid droplets <1%



Kayser et al. JAP 1996
Hoppeler et al. Int J Sports Med 1986

Muscle composition

PROTEINS

p-lipids

glycogen

nucleic acids

Kayser et al. JAP 1996
Hoppeler et al. Int J Sports Med 1986

Energy cost

Na^+/K^+ pumps

SERCA (Ca^{2+} pumps)

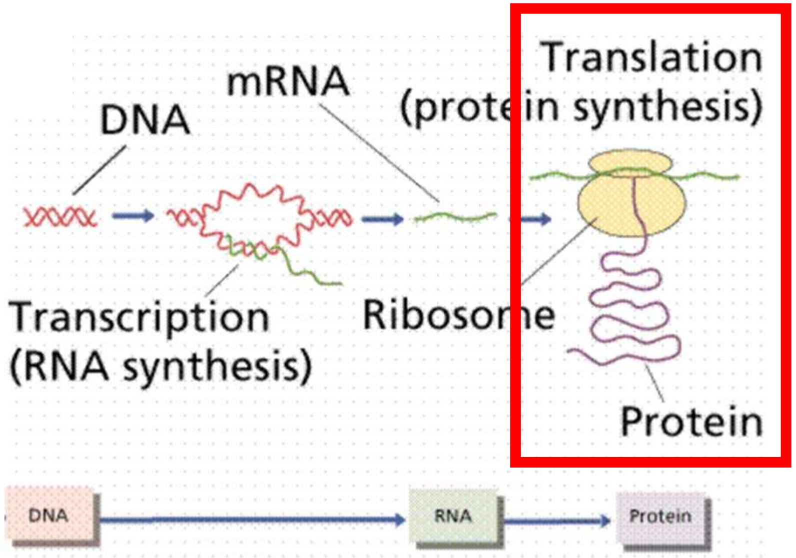
myosin ATPase

biosynthesis

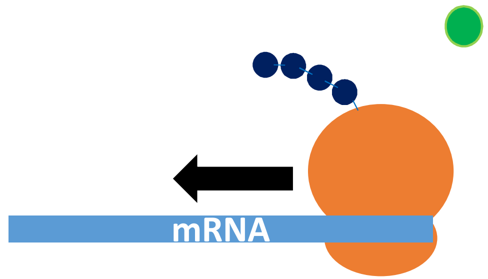
nucleic acids <<< proteins

Proud Biochem J 2007
Smith Plos One 2013

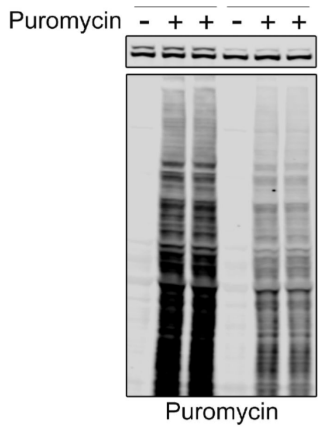
Protein synthesis



Puromycin

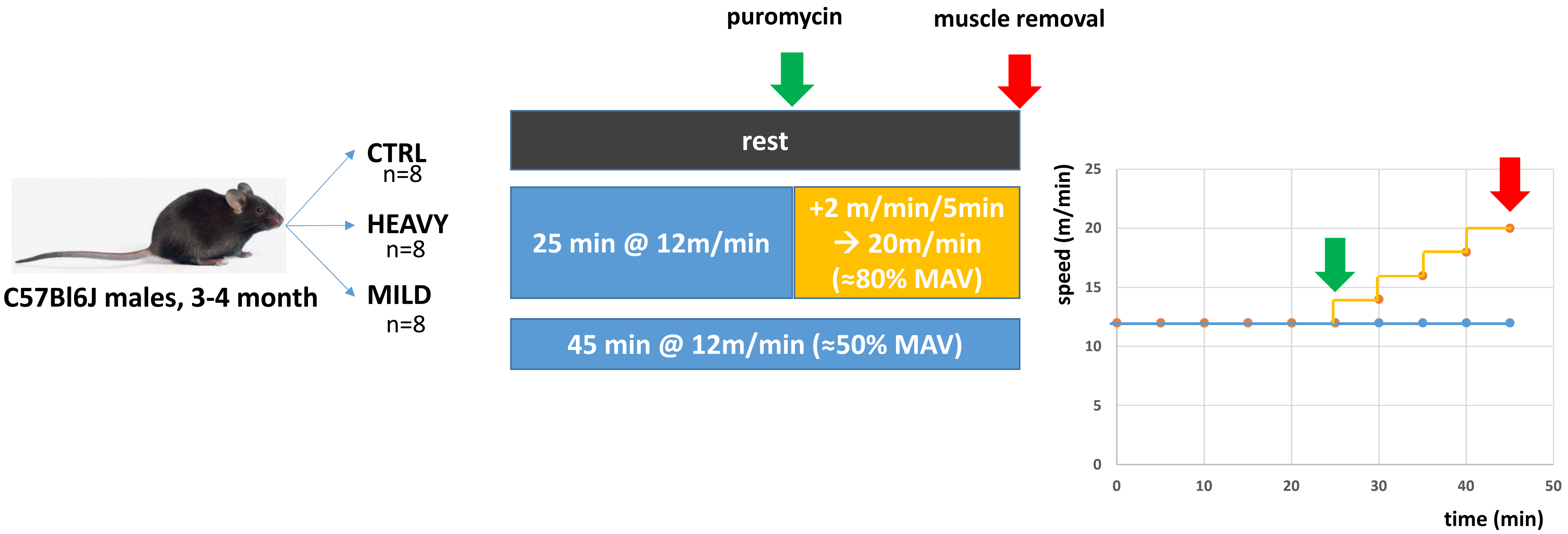


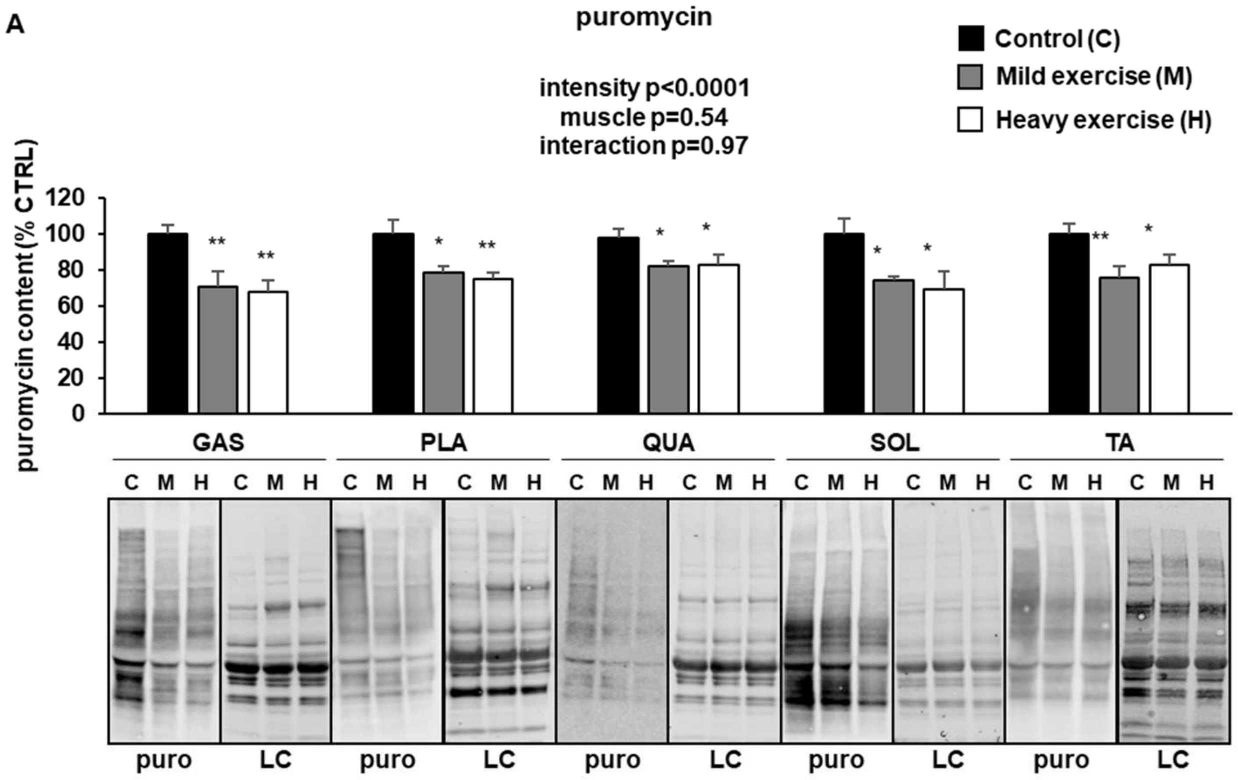
+ Western Blot / IF

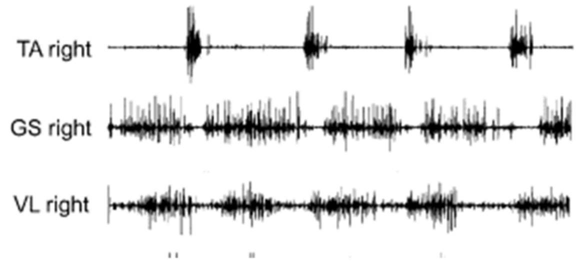


How protein translation is altered by endurance exercise in mice ?

Intensity- and/or muscle-dependent?



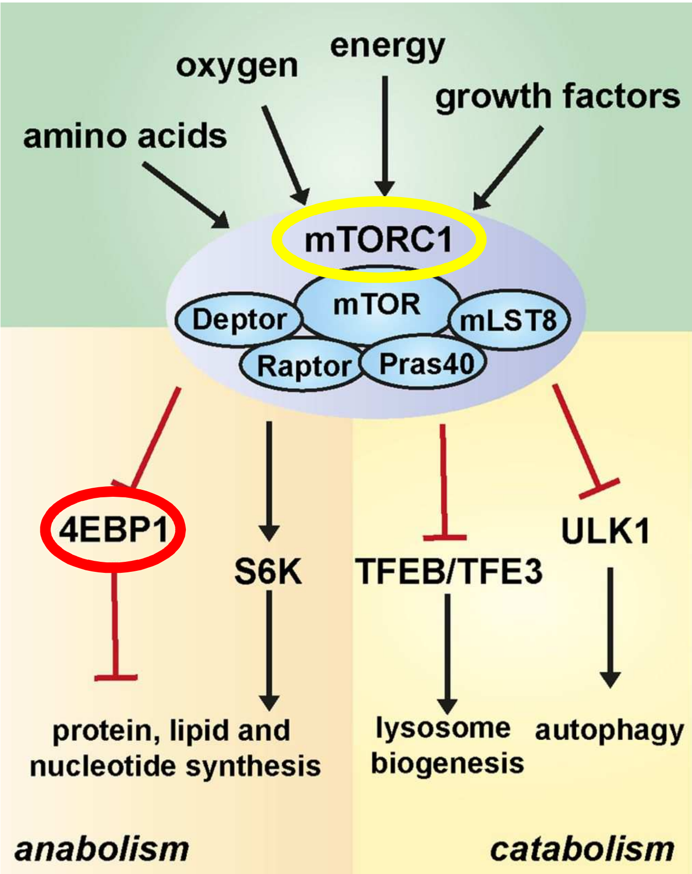


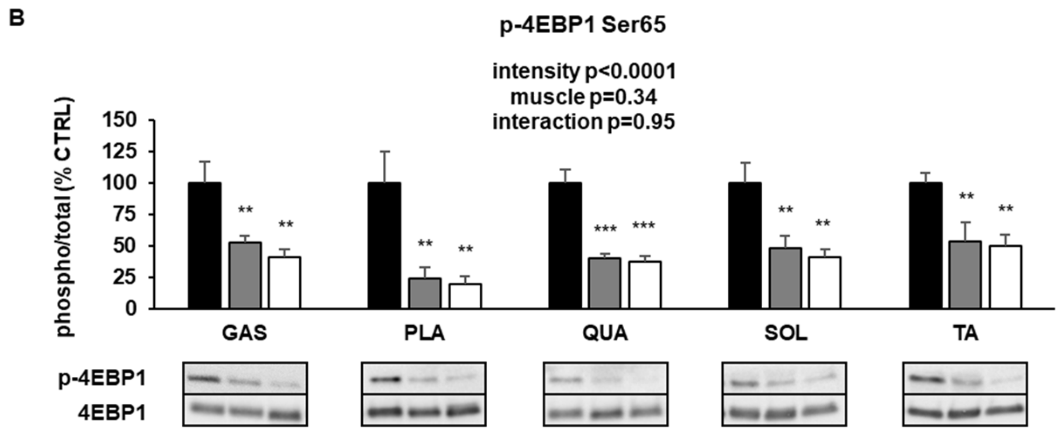


Pearson et al., J Neurosci Methods 2005

- ➢ **Light intensity exercise reduces protein translation**
- ➢ **No effect of exercise intensity**
- ➢ **No effect of muscle type**

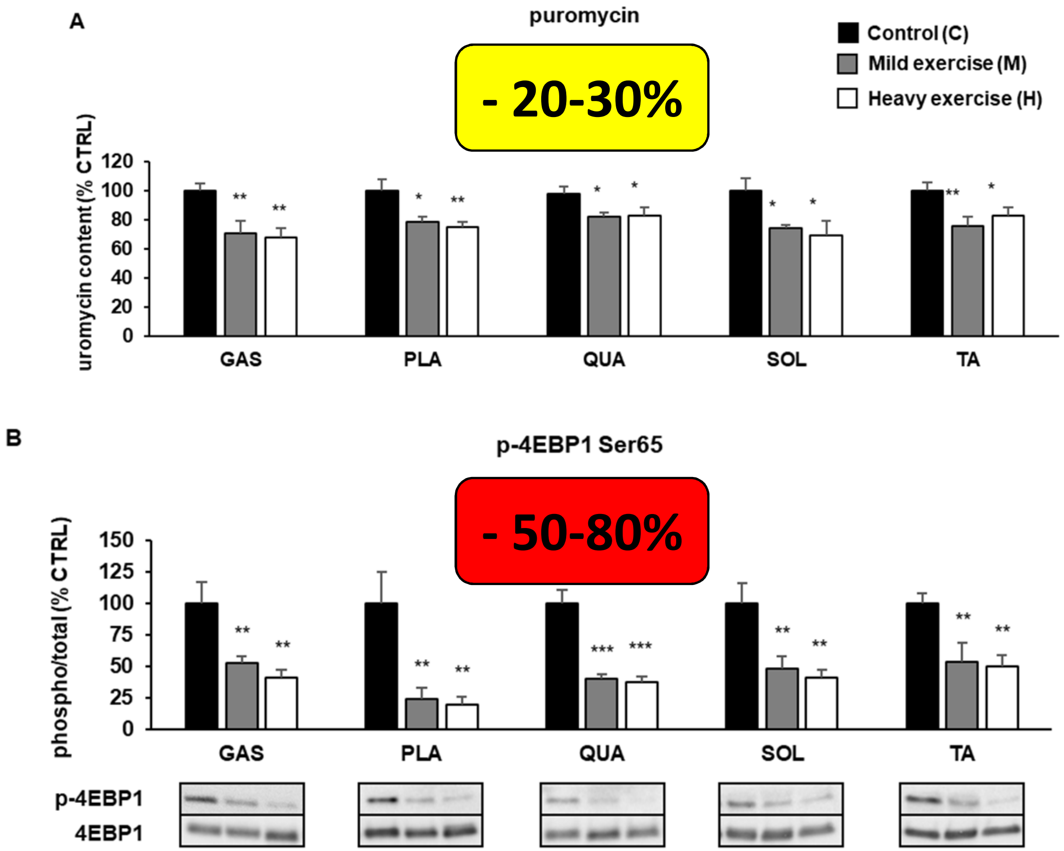
Regulation of protein synthesis

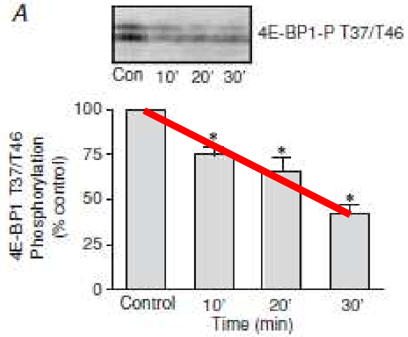




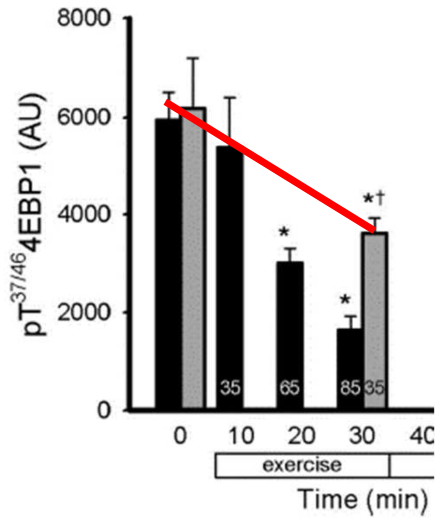
- Marked inhibition of TORC1 activity
- No effect of exercise intensity
- No effect of muscle type

Regulation of protein synthesis

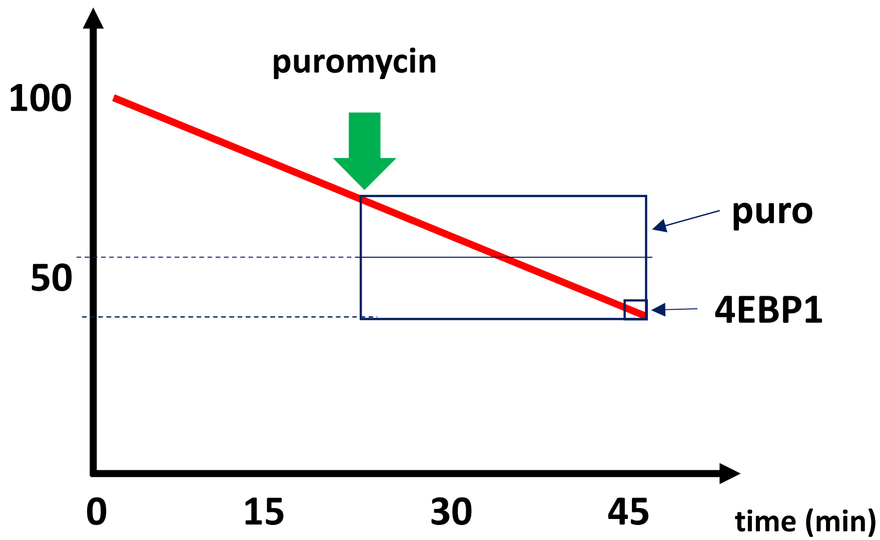


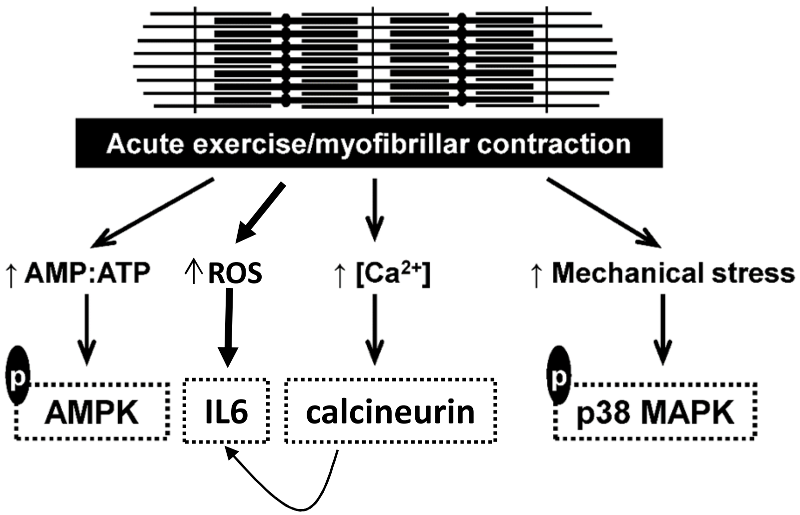


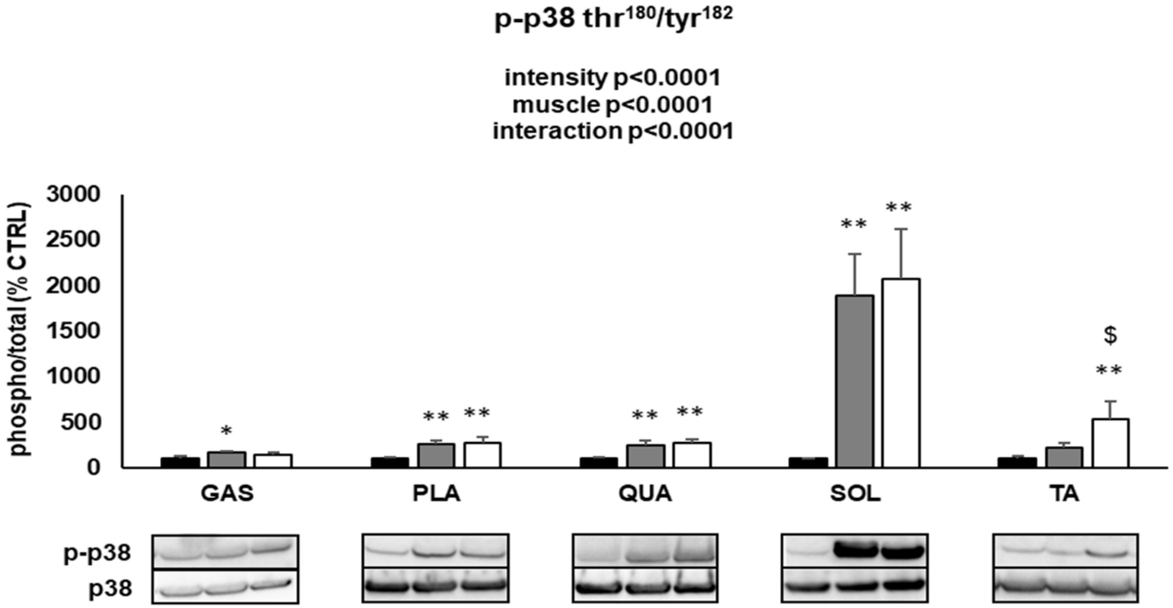
Williamson et al., J Physiol 2006



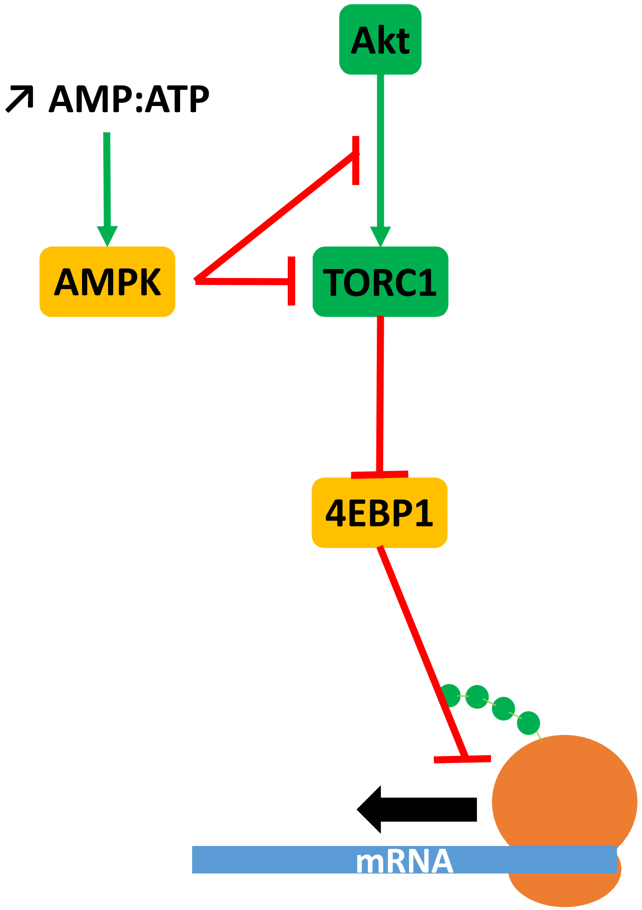
Rose et al., AJP 2009



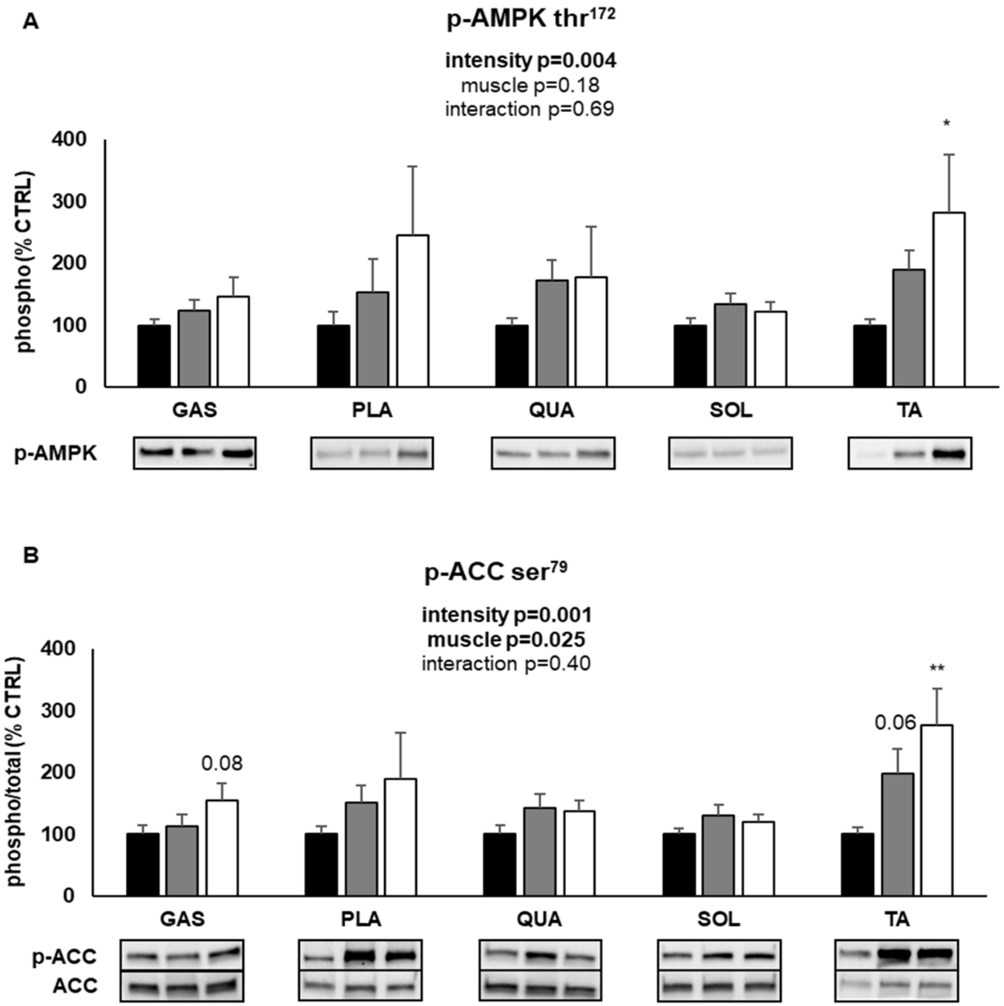




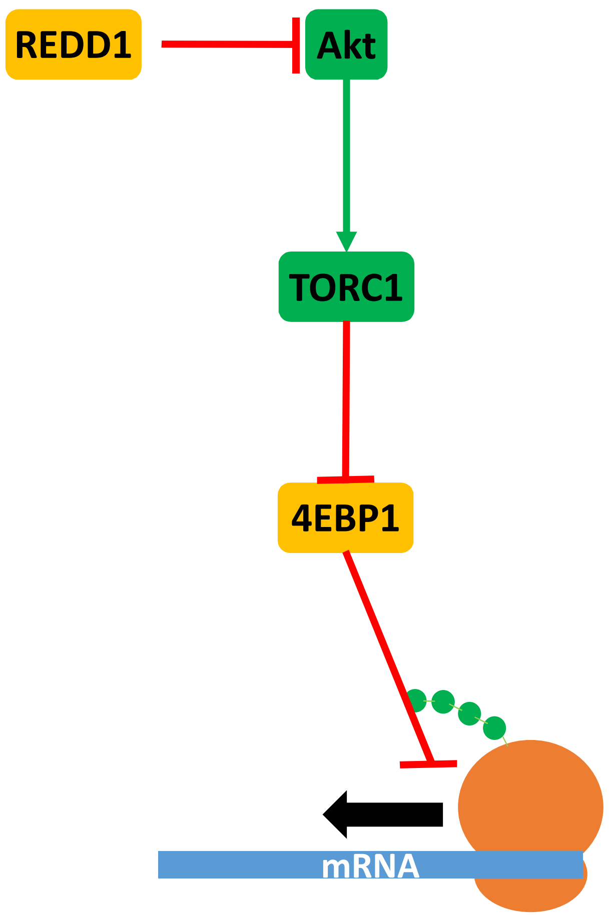
- High p38 activation… particularly in SOL
- No effect of exercise intensity (except for TA)

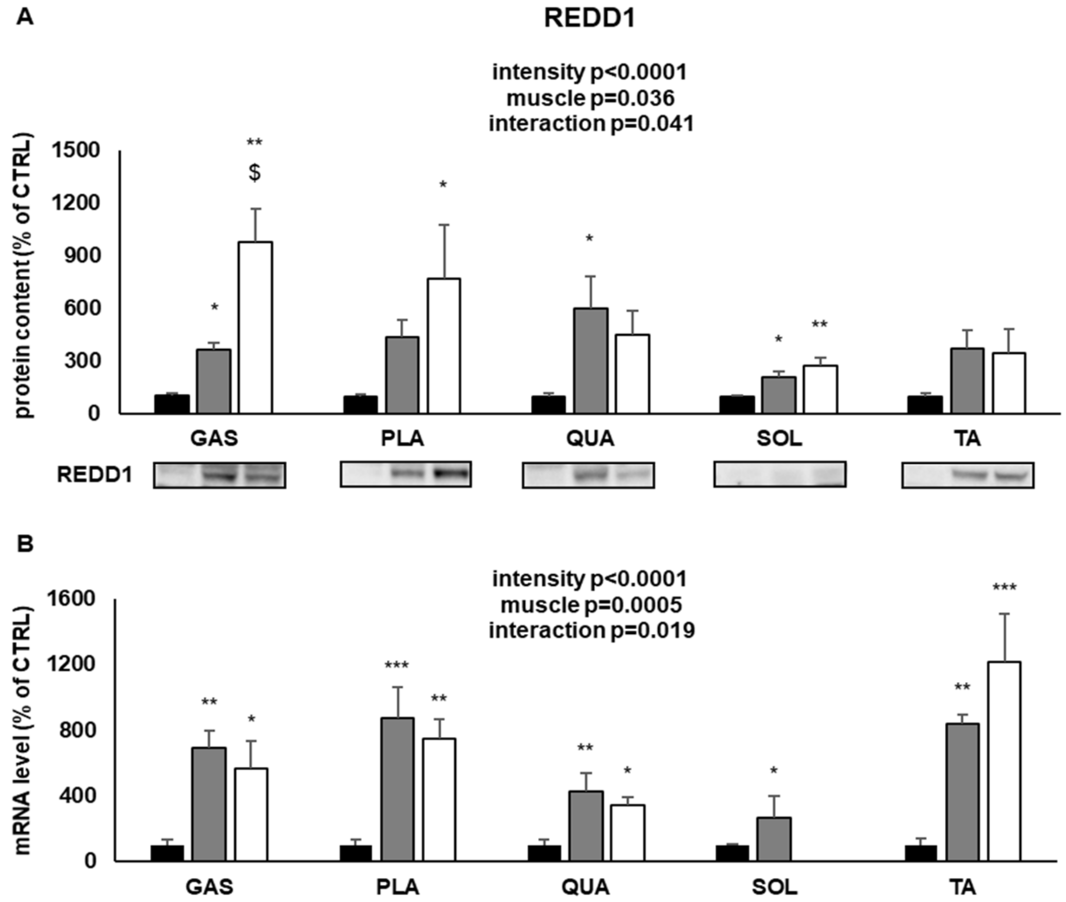


↗ AMP:ATP
Akt
AMPK
TORC1
4EBP1
mRNA

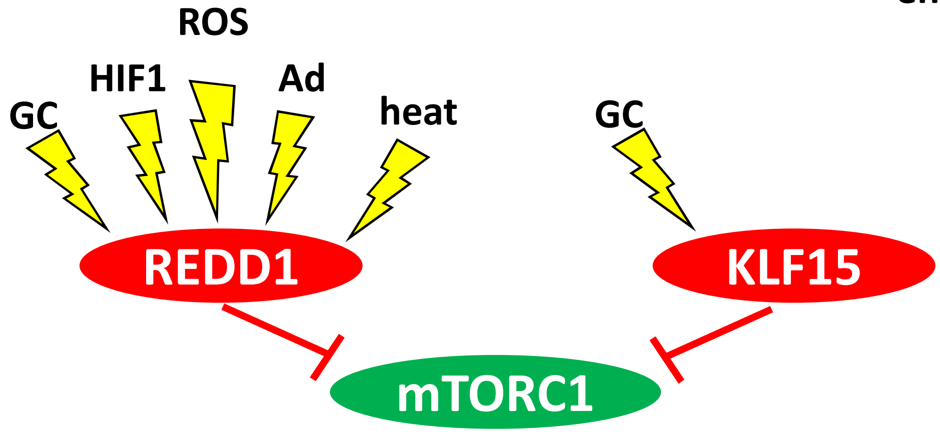


A
p-AMPK thr172
intensity p=0.004
muscle p=0.18
interaction p=0.69
phospho (% CTRL)
400
300
200
100
0
*
GAS
PLA
QUA
SOL
TA
p-AMPK
B
p-ACC ser79
intensity p=0.001
muscle p=0.025
interaction p=0.40
phospho/total (% CTRL)
400
300
200
100
0
0.08
0.06
**
GAS
PLA
QUA
SOL
TA
p-ACC
ACC

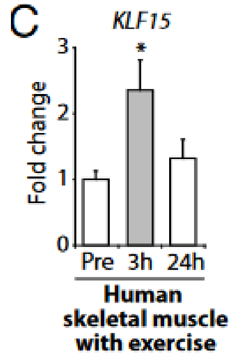

REDD1
Akt
TORC1
4EBP1
mRNA


A
REDD1
intensity p<0.0001
muscle p=0.036
interaction p=0.041
protein content (% of CTRL)
GAS
PLA
QUA
SOL
TA
REDD1
B
intensity p<0.0001
muscle p=0.0005
interaction p=0.019
mRNA level (% of CTRL)
GAS
PLA
QUA
SOL
TA

endurance exercise
fasting

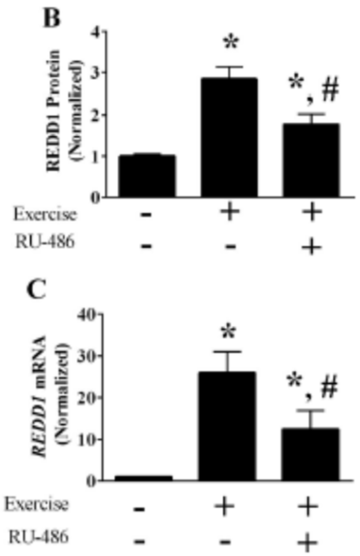


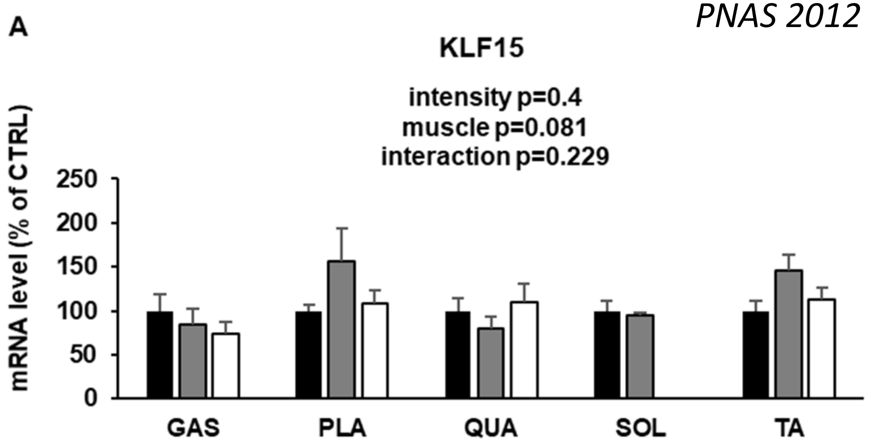
endurance exercise
fasting



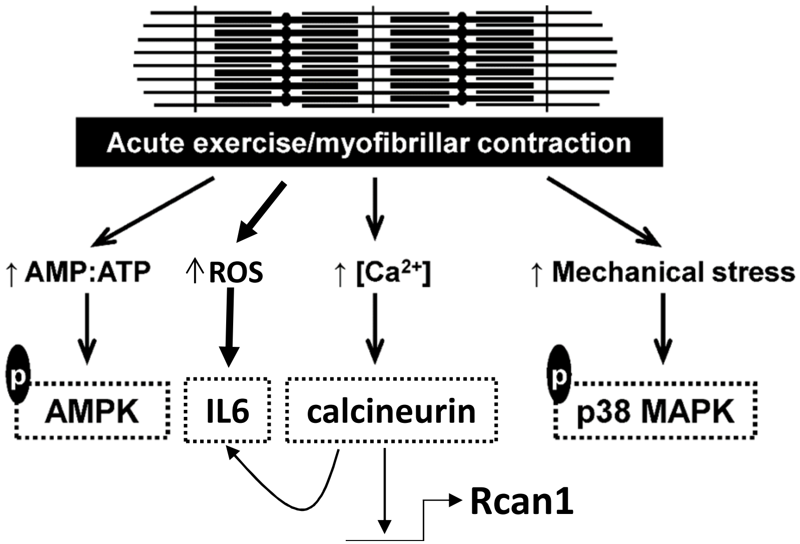
Haldar & al.
PNAS 2012

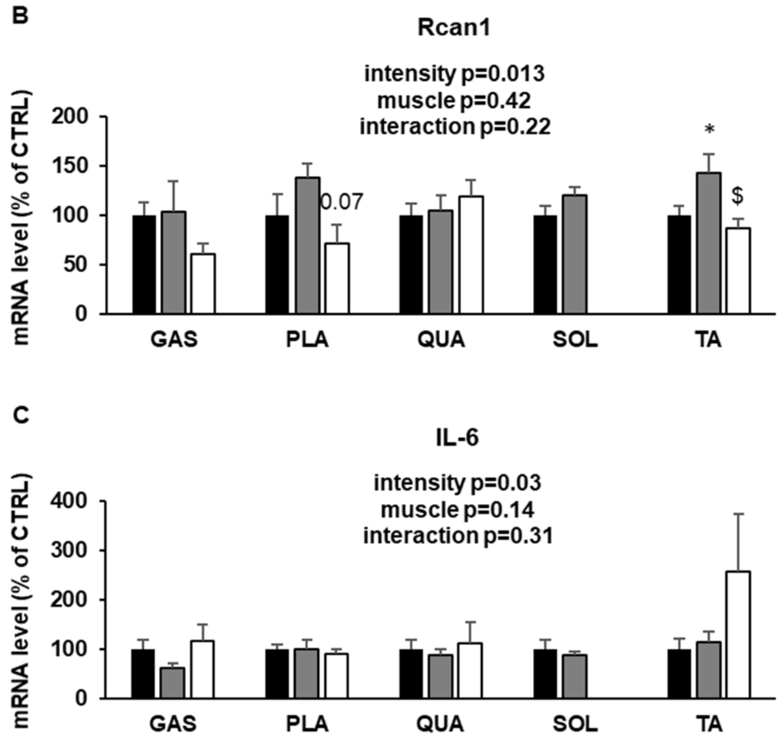
1h post ex

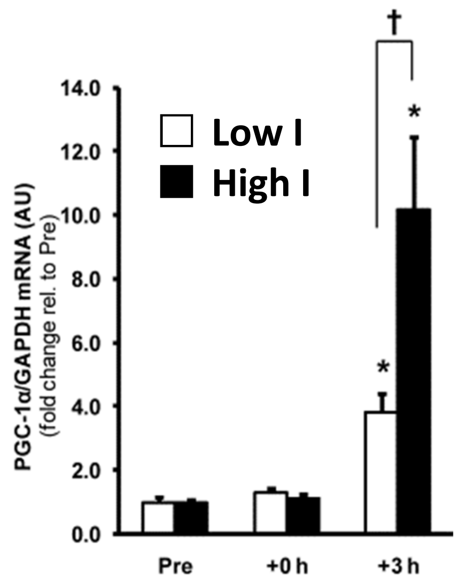




Gordon & al. AJPEM 2017





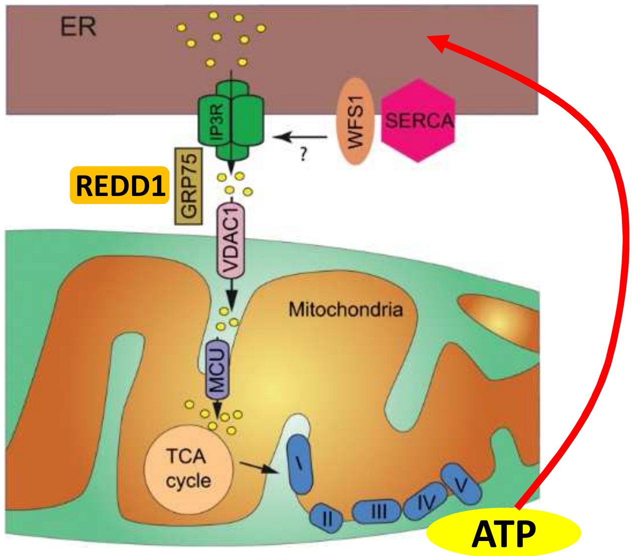


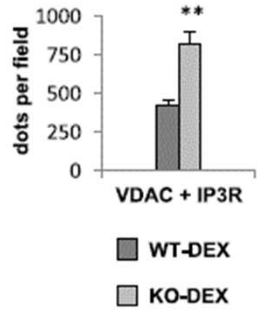
Egan & al. J Physiol 2010

➢ **Very few gene induction during exercise… except REDD1!**
=> REDD1 required for cell adaptation DURING exercise?

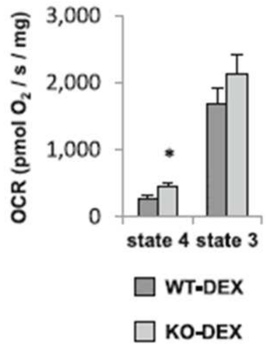
SR => 30% ATP during muscle contraction

protein & p-lipids synthesis

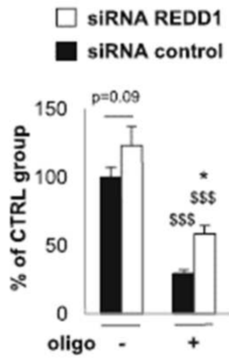




➢ **REDD1 dirupts SR/mito**



➢ **REDD1 reduces mito respiration**

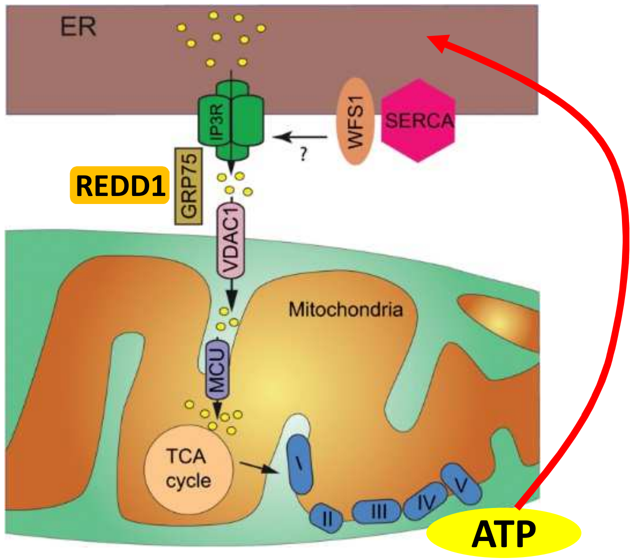


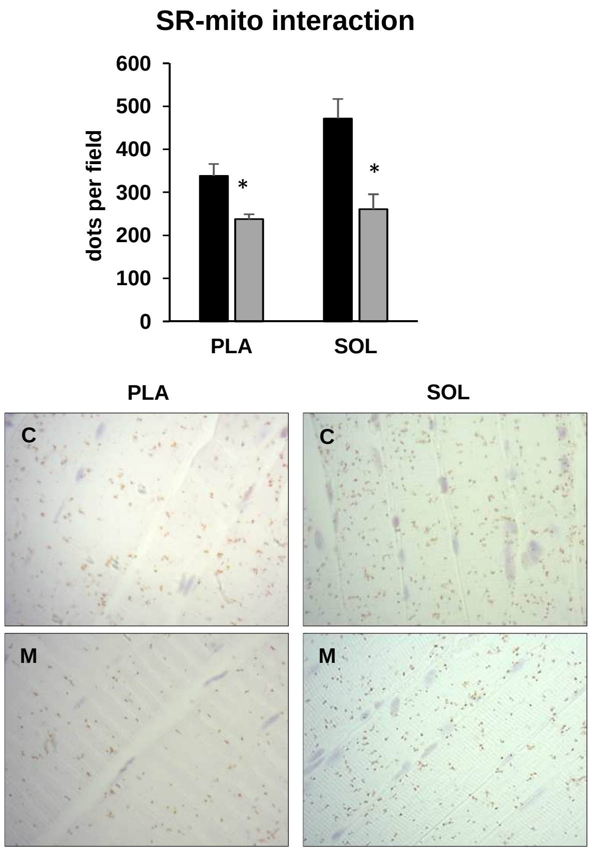
➢ **REDD1 reduces protein synthesis**

Britto & al. BMC Biol 2018

SR => 30% ATP during muscle contraction

protein & p-lipids synthesis



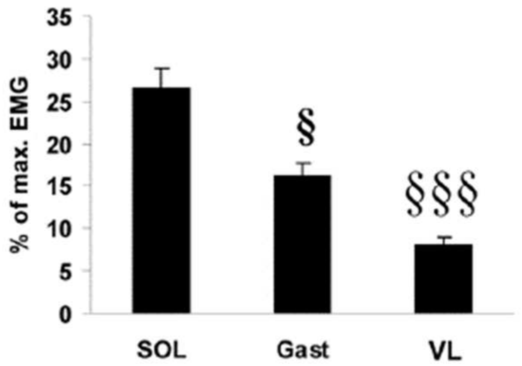


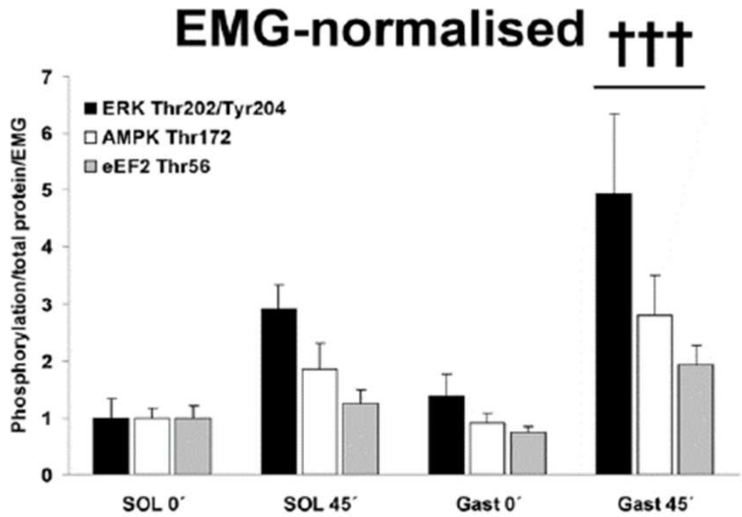
➢ **Mild intensity aerobic exercise dirupts SR-mitochondria interaction**

<u>**CONCLUSIONS (1/3)**</u>

- **Light intensity exercise reduces protein translation**
- **No differences between muscles**

15% incline, 70% VO2max



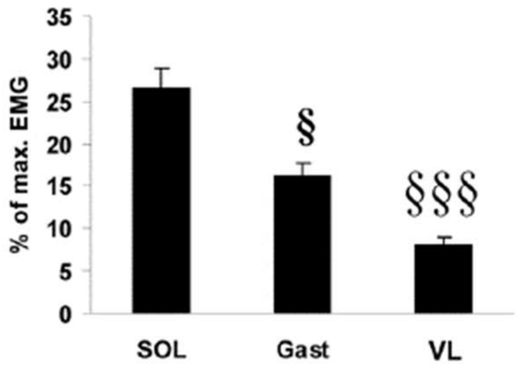


Jensen & al. PlosOne 2012

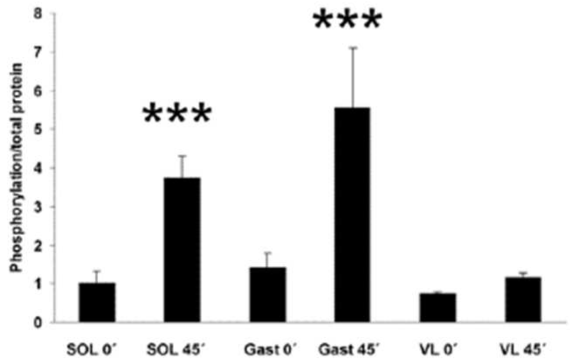
CONCLUSIONS (1/3)

- **Light intensity exercise reduces protein translation**
- **No differences between muscles**

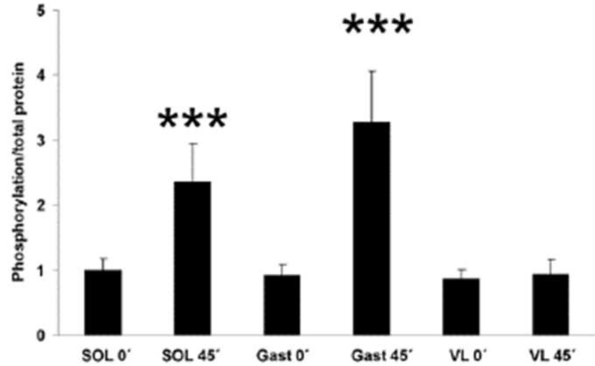
15% incline, 70% VO2max



ERK 1/2 Thr202/Tyr204



AMPK Thr172

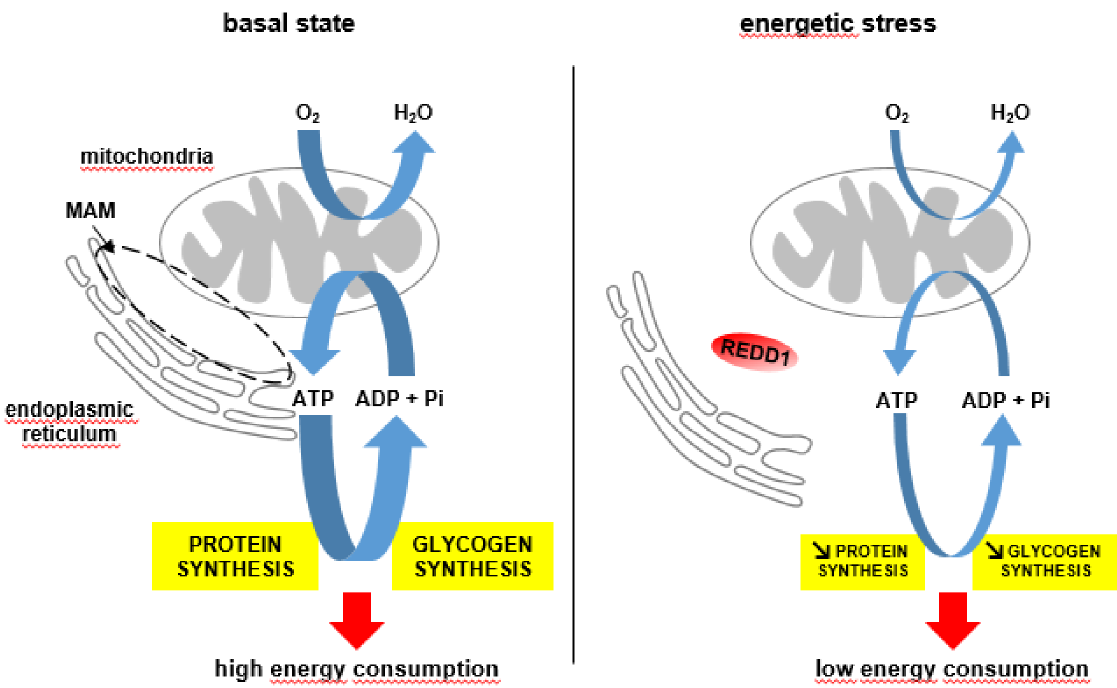


- **the more activated, the more resistant (and vice versa)?**

Jensen & al. PlosOne 2012

CONCLUSIONS (2/3)

- Light intensity exercise reduces protein translation
- No differences between muscles
- Related to REDD1 expression and mito/SR disruption

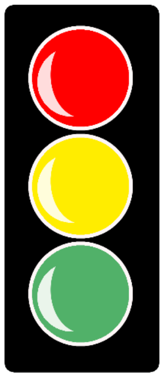


CONCLUSIONS (3/3)

- Light intensity exercise reduces protein translation
- No differences between muscles
- Related to REDD1 expression and mito/SR disruption
- REDD1 induction precedes AMPK activation?

Crisis ??!!
We need AMPK!!!

Nein, nein: austerity!
REDD1 is sufficient

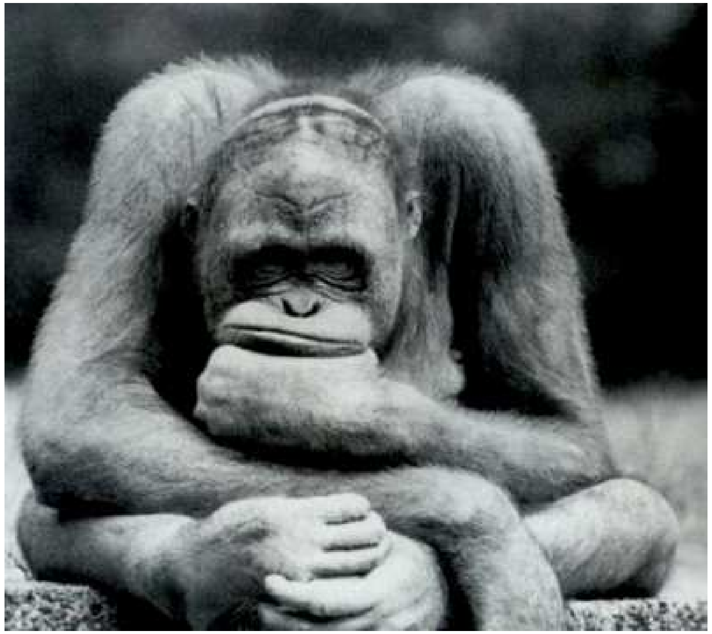


AMPK activation

REDD1 induction

PERSPECTIVES (1/3)

OK and so what?



- What if muscle cells fail to regulate ER/mito interaction?

$\Rightarrow$ ER stress

  - altered adaptations to training (anabolic resistance)
  - cell dysfunction
  - cell death…

PERSPECTIVES (2/3)

➢ **Beneficial effects of exercise on health are related to ER stress**

J. Phys. Ther. Sci.
27: 3063–3068, 2015

Original Article

Effect of the low- versus high-intensity exercise training on endoplasmic reticulum stress and GLP-1 in adolescents with type 2 diabetes mellitus

Am J Physiol Heart Circ Physiol 310: H279–H289, 2016.
First published November 13, 2015; doi:10.1152/ajpheart.00448.2015.

High-intensity training reduces intermittent hypoxia-induced ER stress and myocardial infarct size

Eur J Appl Physiol (2011) 111:2015–2023
DOI 10.1007/s00421-010-1802-2

ORIGINAL ARTICLE

Endurance exercise training ameliorates insulin resistance and reticulum stress in adipose and hepatic tissue in obese rats

Ability to regulate

ER/mito interaction?

//

Metabolic flexibility?

PERSPECTIVES (3/3)

Area-Gomez *et al. Cell Death and Disease* (2018)9:335
DOI 10.1038/s41419-017-0215-0
Cell Death & Disease

REVIEW ARTICLE Open Access

A key role for MAM in mediating mitochondrial dysfunction in Alzheimer disease

Gómez-Suaga *et al. Cell Death and Disease* 20189:337
DOI 10.1038/s41419-017-0079-3
Cell Death & Disease

REVIEW ARTICLE Open Access

ER–mitochondria signaling in Parkinson's disease

➢ Target ER/mito interaction as a therapeutic approach

Depressing Mitochondria-Reticulum Interactions Protects Cardiomyocytes From Lethal Hypoxia-Reoxygenation Injury

Disruption of Mitochondria-Associated Endoplasmic Reticulum Membrane (MAM) Integrity Contributes to Muscle Insulin Resistance in Mice and Humans

- **Infarct?**
- **Neurodegenerative diseases?**
- **T2D/obesity?**
- **Cancer ?**
- **Sickle Cell Disease?**

Review

ER-mitochondria interactions: Both strength and weakness within cancer cells

"MAM represent both a hot spot in cancer onset and progression and an Achilles' heel of cancer cells that can be exploited for therapeutic perspectives."

frontiers in Cellular Neuroscience

ORIGINAL RESEARCH
published: 19 February 2019
doi: 10.3389/fncel.2019.00056

Check for updates

Mast Cells Induce Blood Brain Barrier Damage in SCD by Causing Endoplasmic Reticulum Stress in the Endothelium

"Targeting mast cells and/or ER stress has the potential to ameliorate endothelial dysfunction in SCD and other pathobiologies."


C'EST FINI, ÇA Y EST !
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