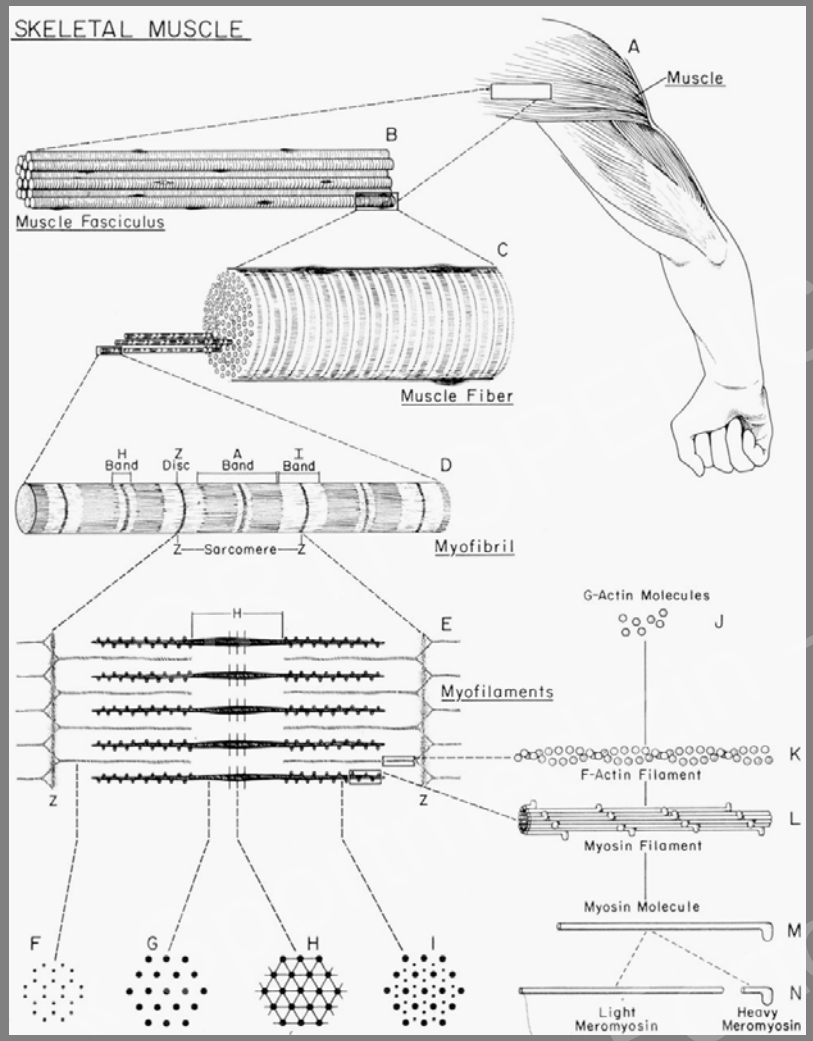
Neuere Molekulare Aspekte der Muskel-physiologie mit Applikationswert

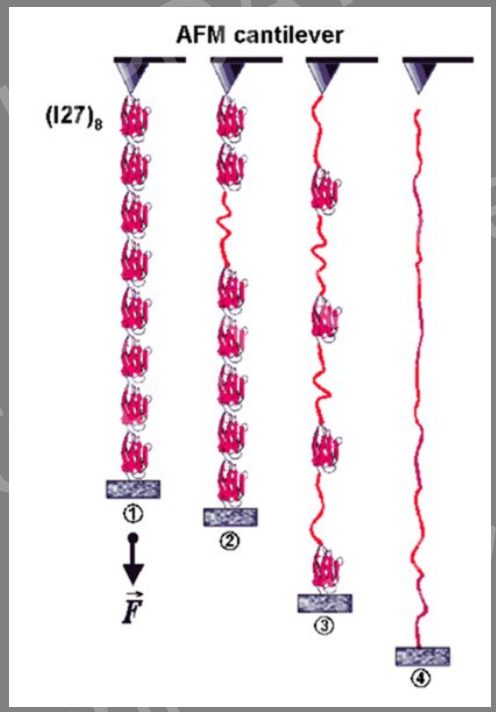
Hans Hoppeler

UNIVERSITÄT BERN



The classical view of muscle

Two recent modifications

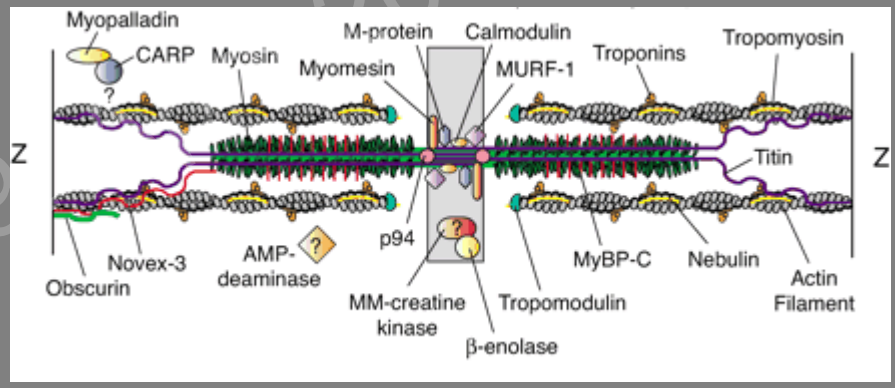


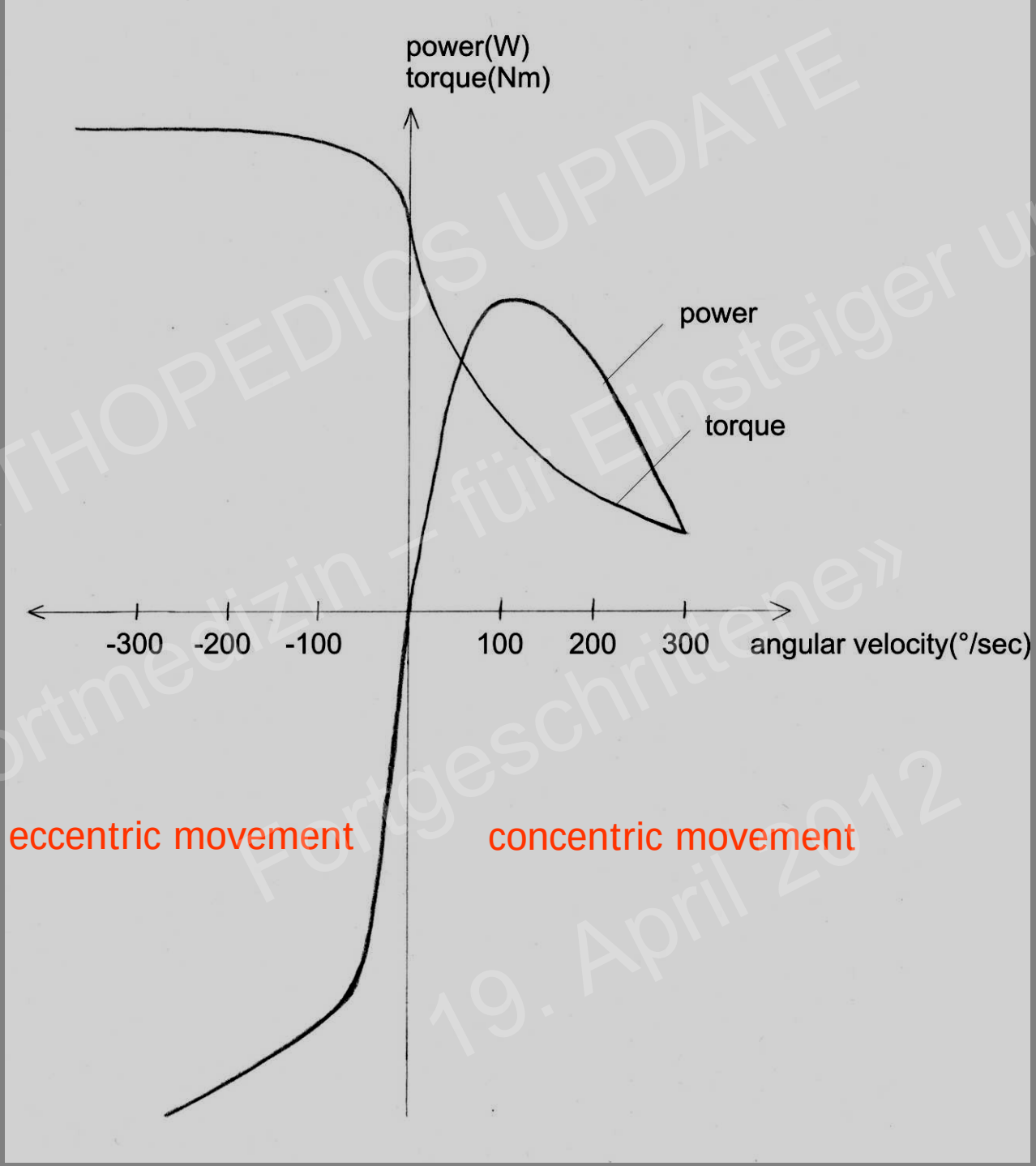
Titin

the third filament responsible for elastic, lenghtening behaviour of muscle

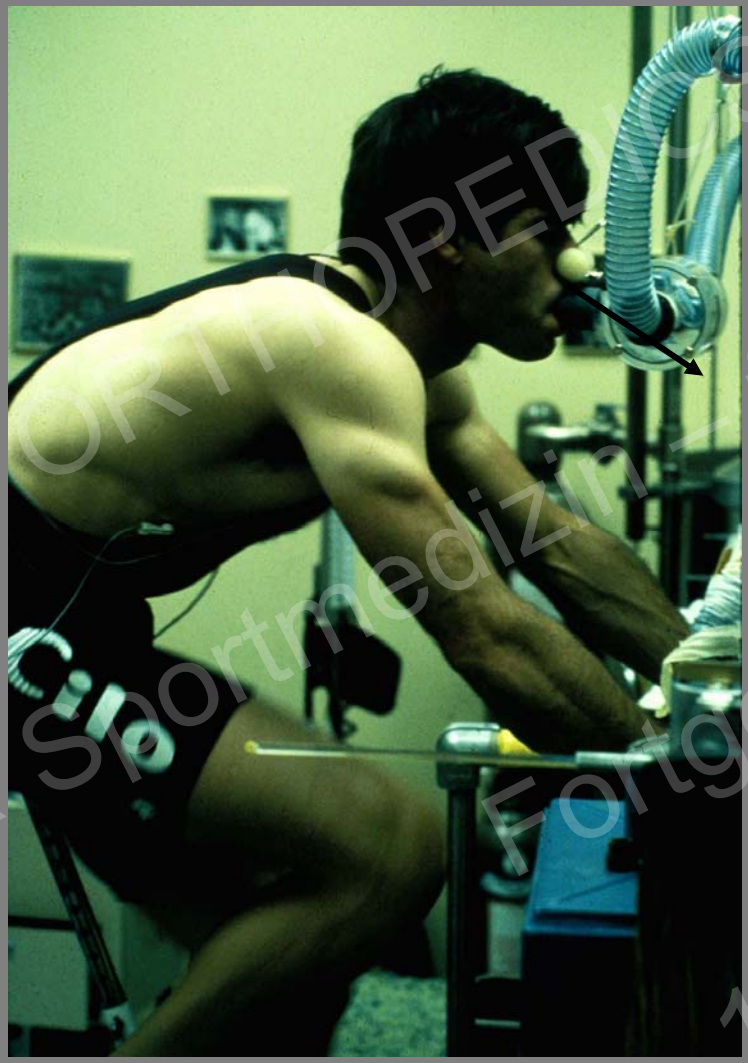
Signaling

Hundreds of proteins functioning in signaling, developmental and mechanical functions

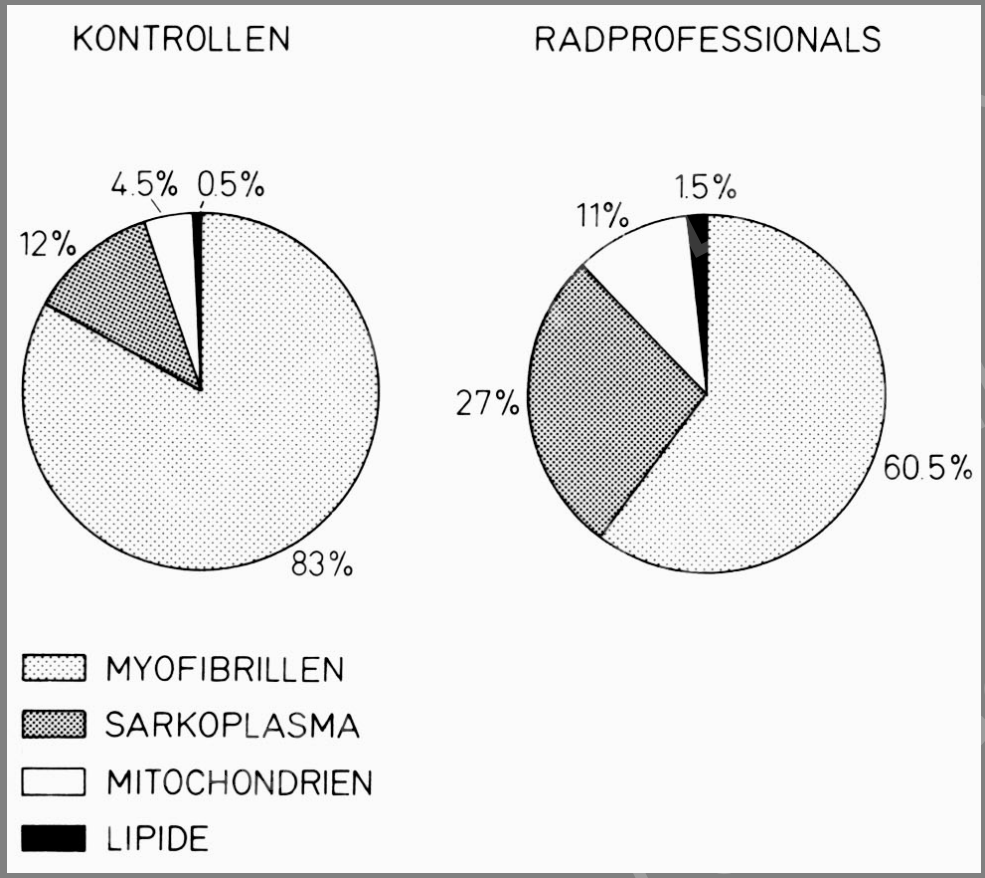


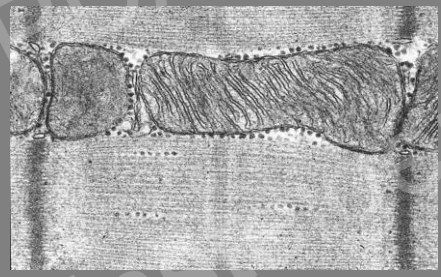


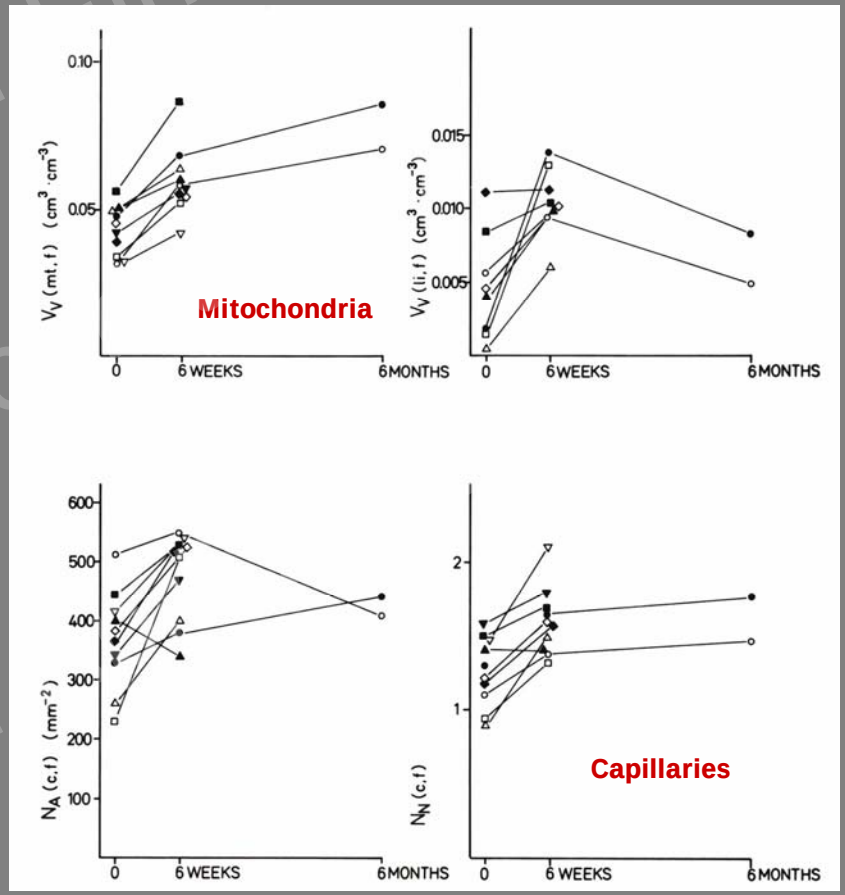
Muscle plasticity with endurance training



Mitochondrial and capillary content of muscle varies massively -





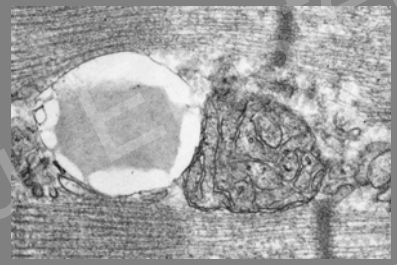


and changes rapidly with exercise

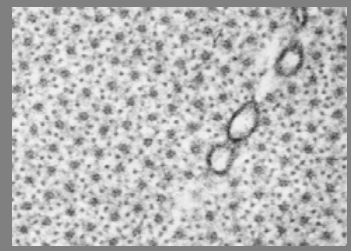
(+40% in 6 weeks of endurance exercise)

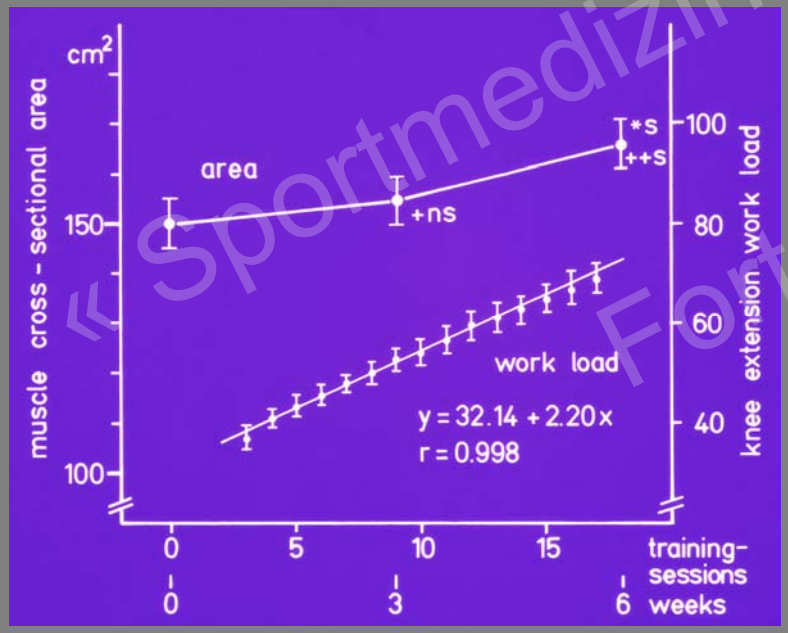
Muscle plasticity with strength training

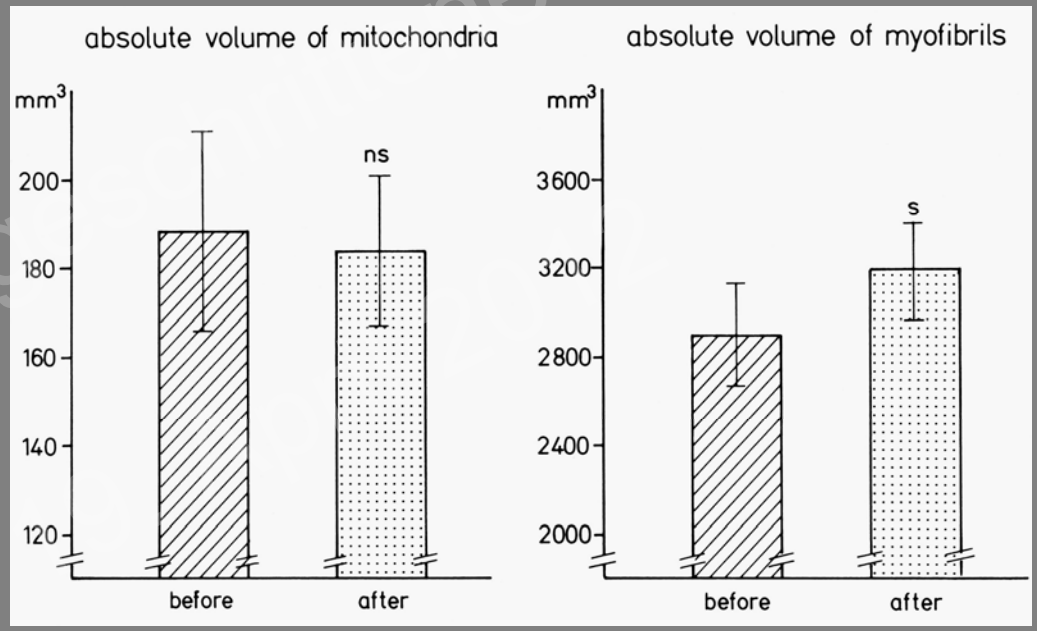
No change in mitochondria



Increase in myofibrils



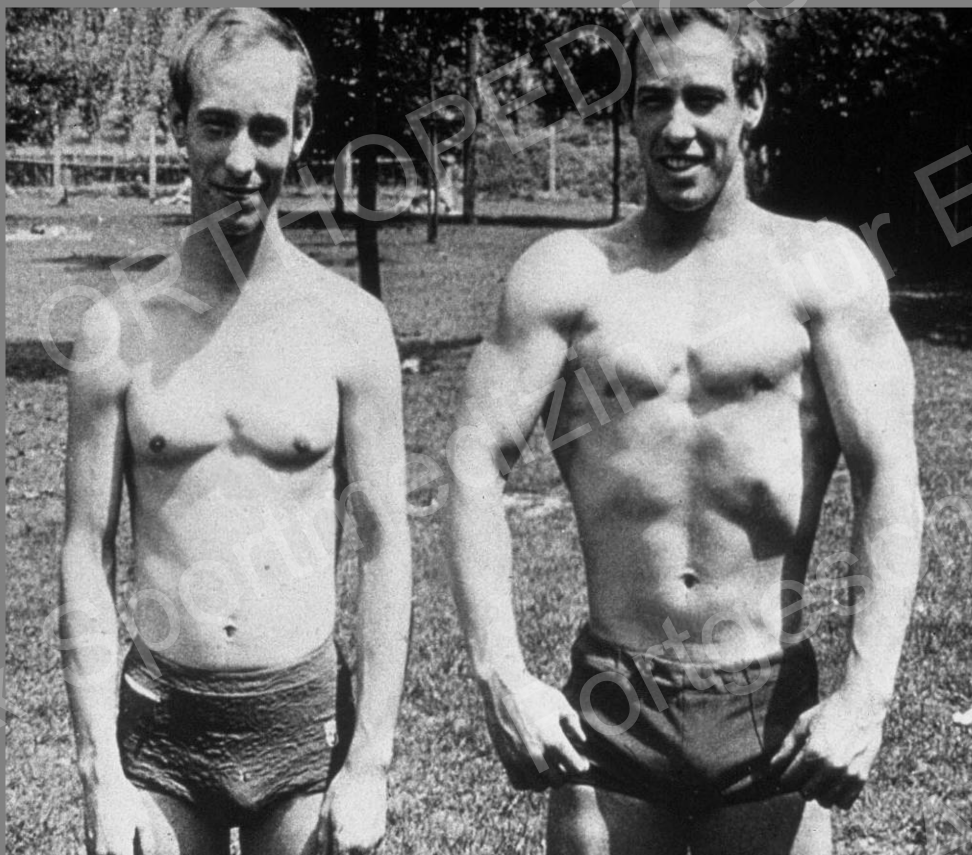




Plus 15 % myofibrils in 6 weeks

Phenotypic plasticity

Kurt Ewald



endurance runner weight lifter

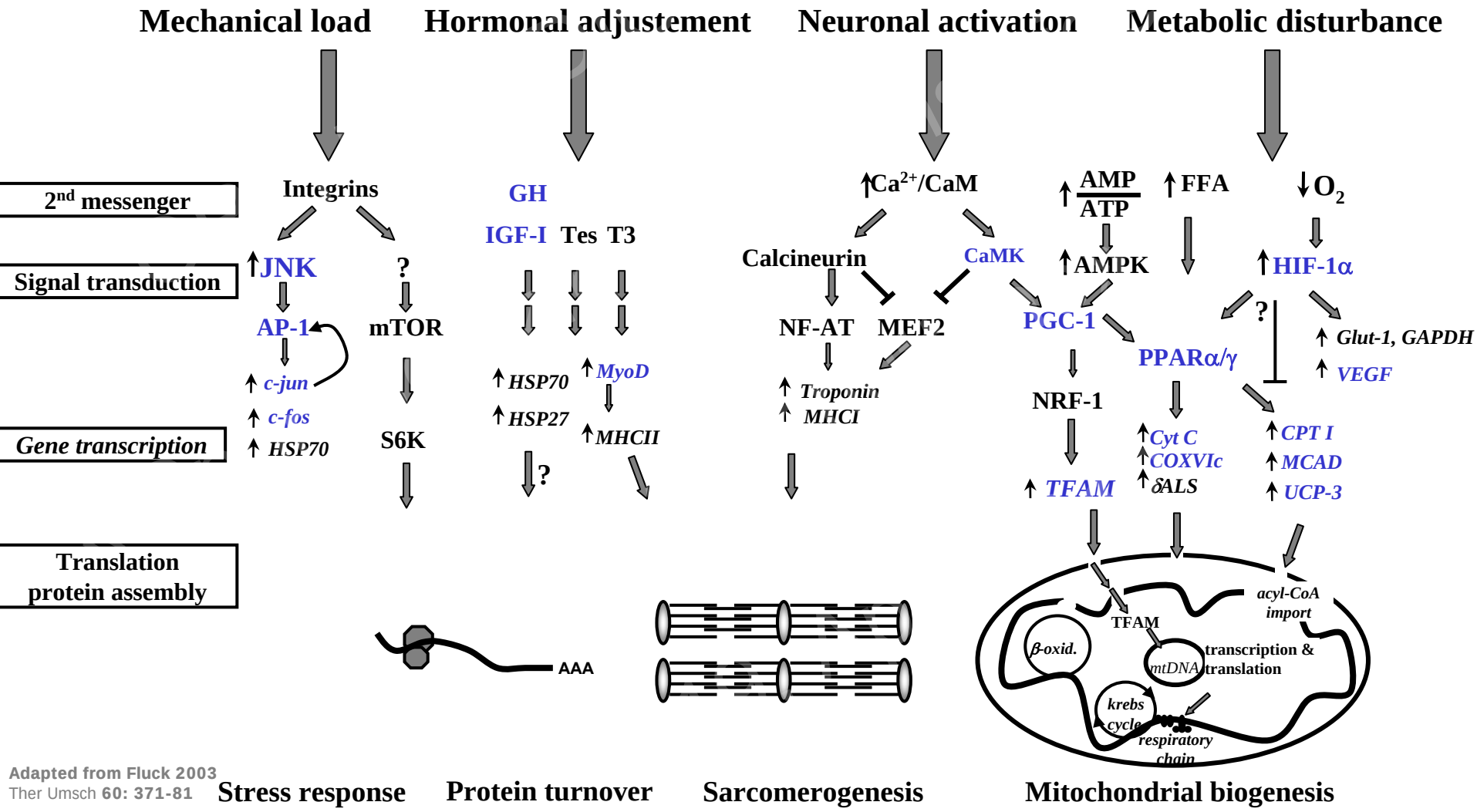
Monozygotic twins:

identical genotype

↓

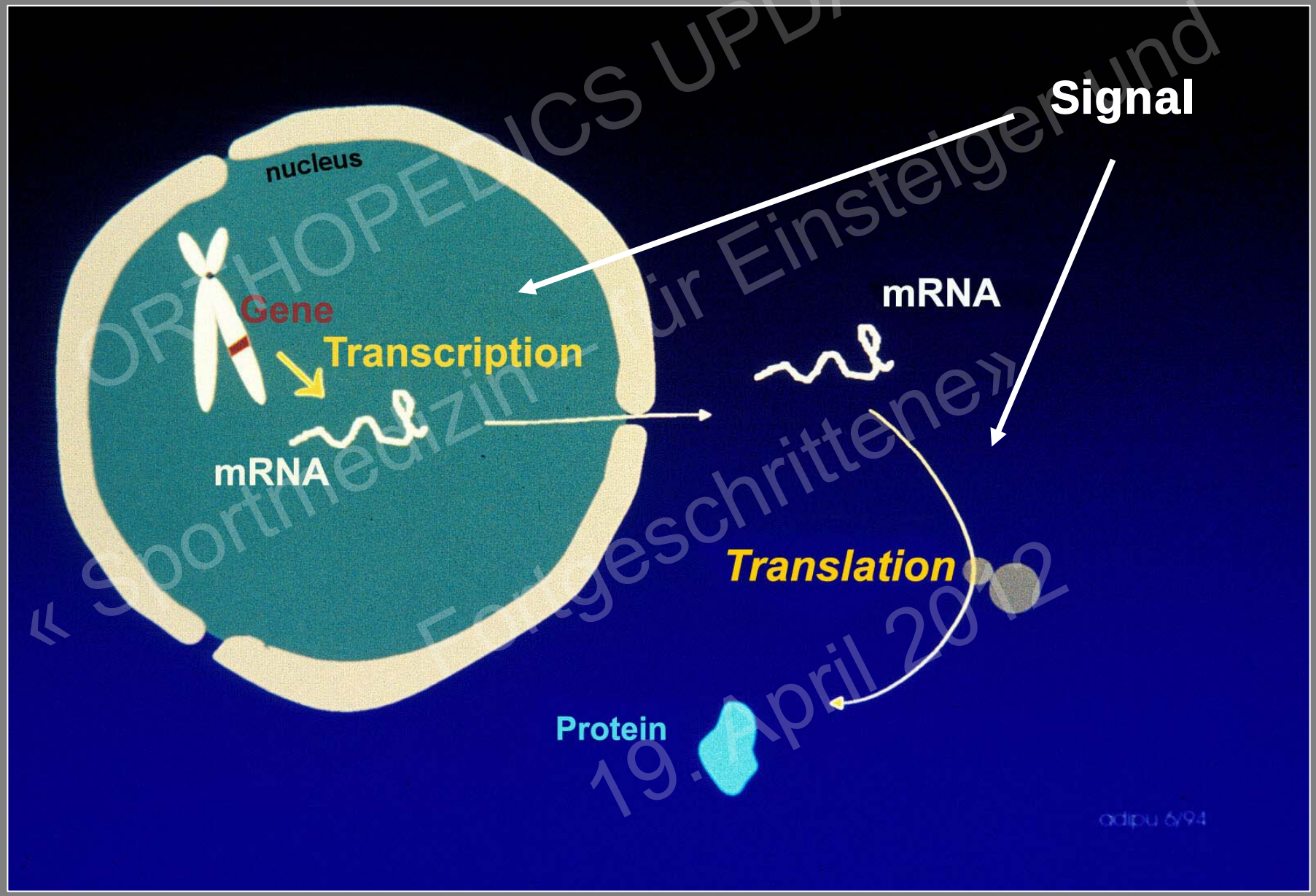
different phenotype
by different training

Signals for muscle adaptation



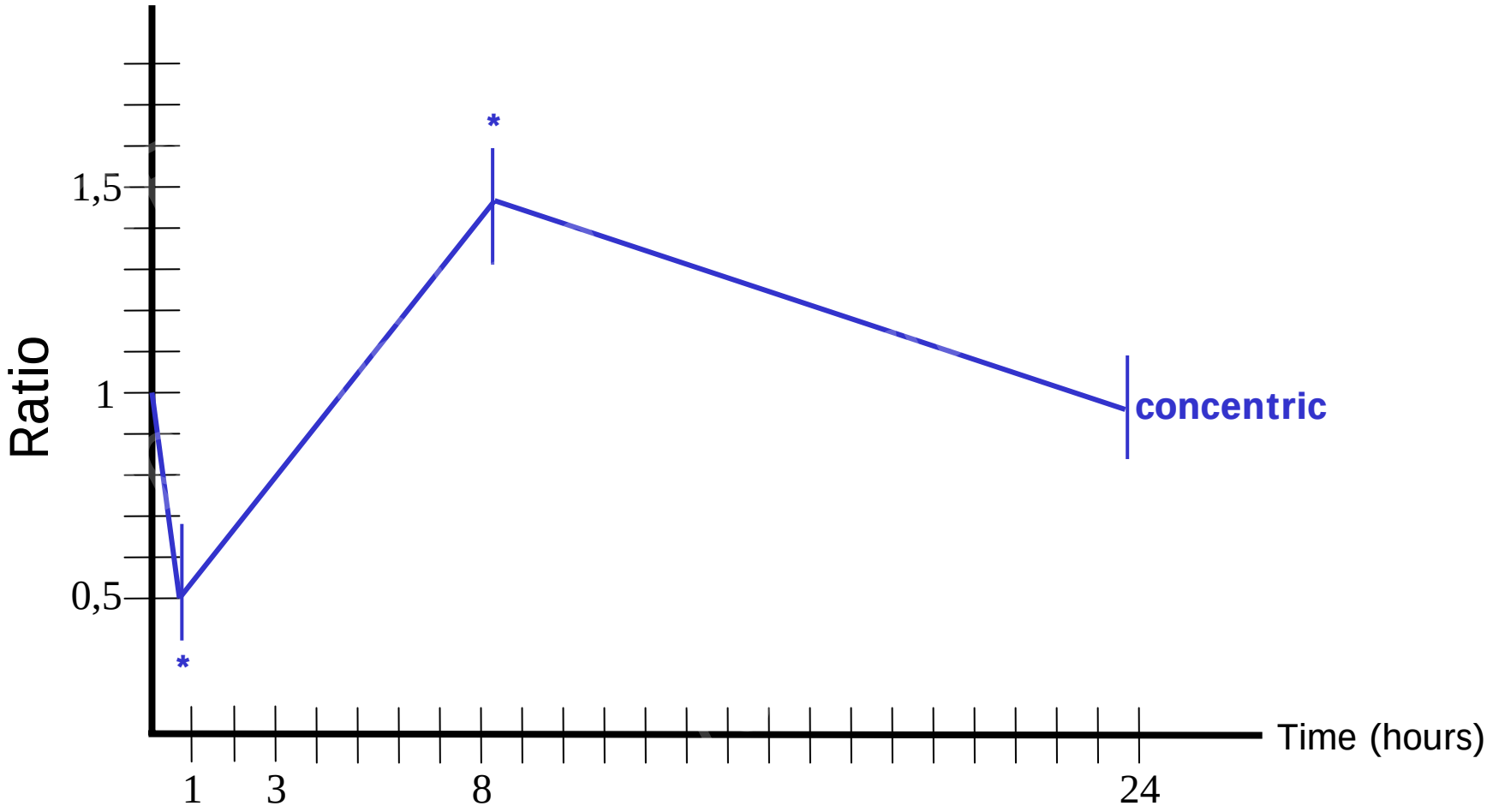
Adapted from Fluck 2003
Ther Umsch 60: 371-81

Mechanism of mitochondrial volume adjustment with exercise ?



Time course of response of muscle transcriptome to 30 min endurance exercise

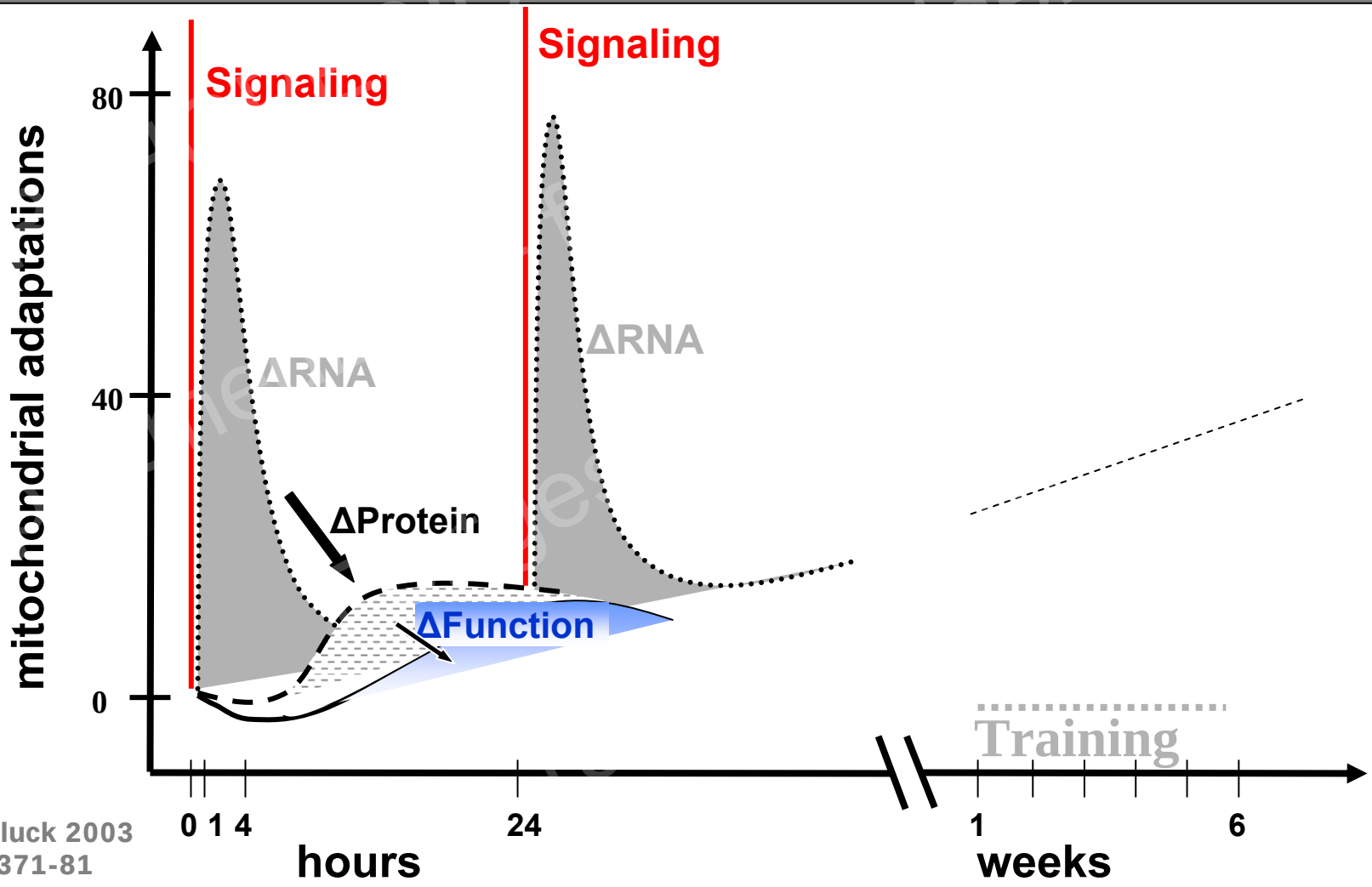
Mean of 220 genes (112 detected concentric)



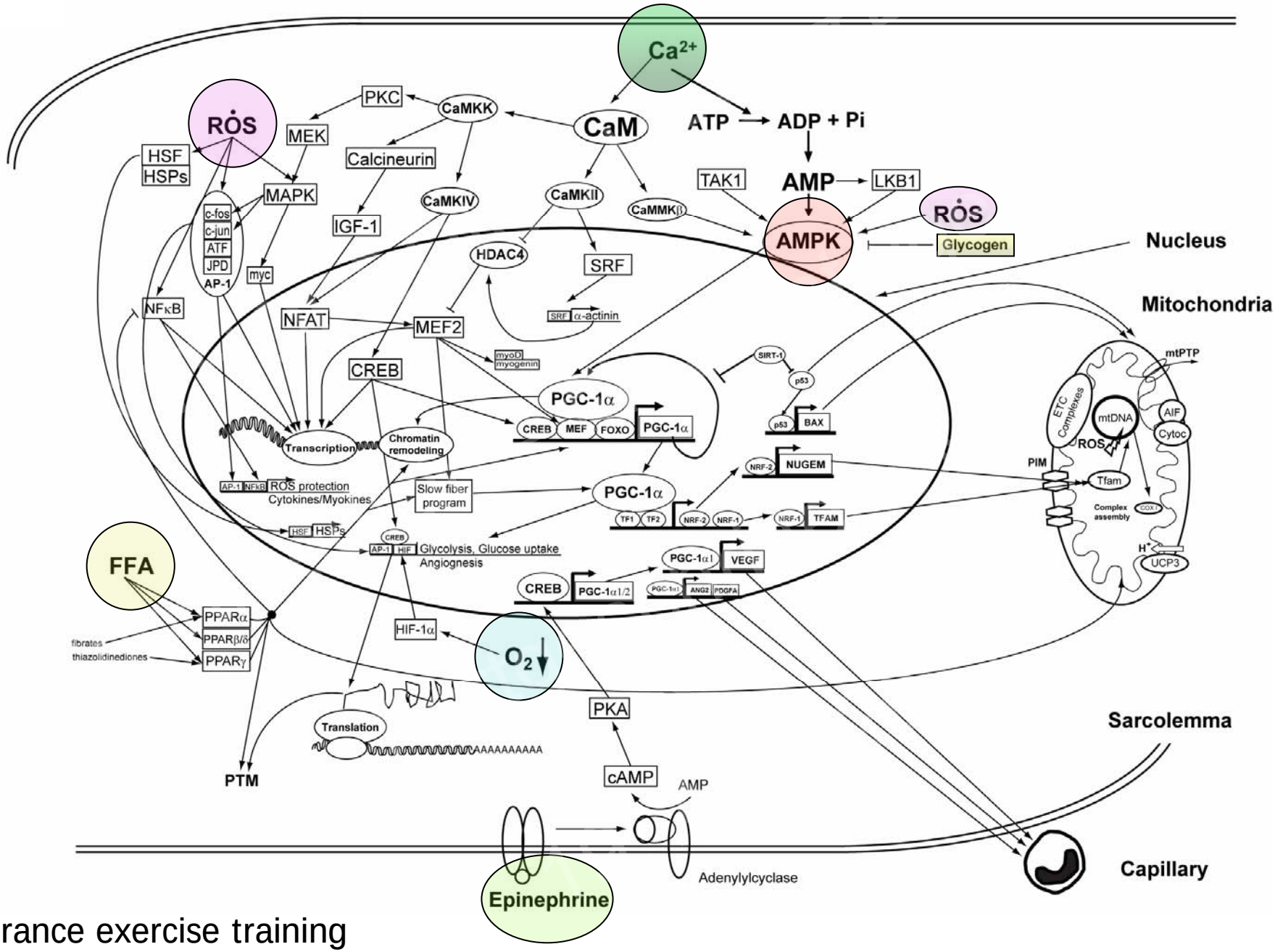
* significantly different from pre-biopsy

Schmutz et al. 2006, Pflügers Arch. 451: 678-687

Response of muscle transcriptome



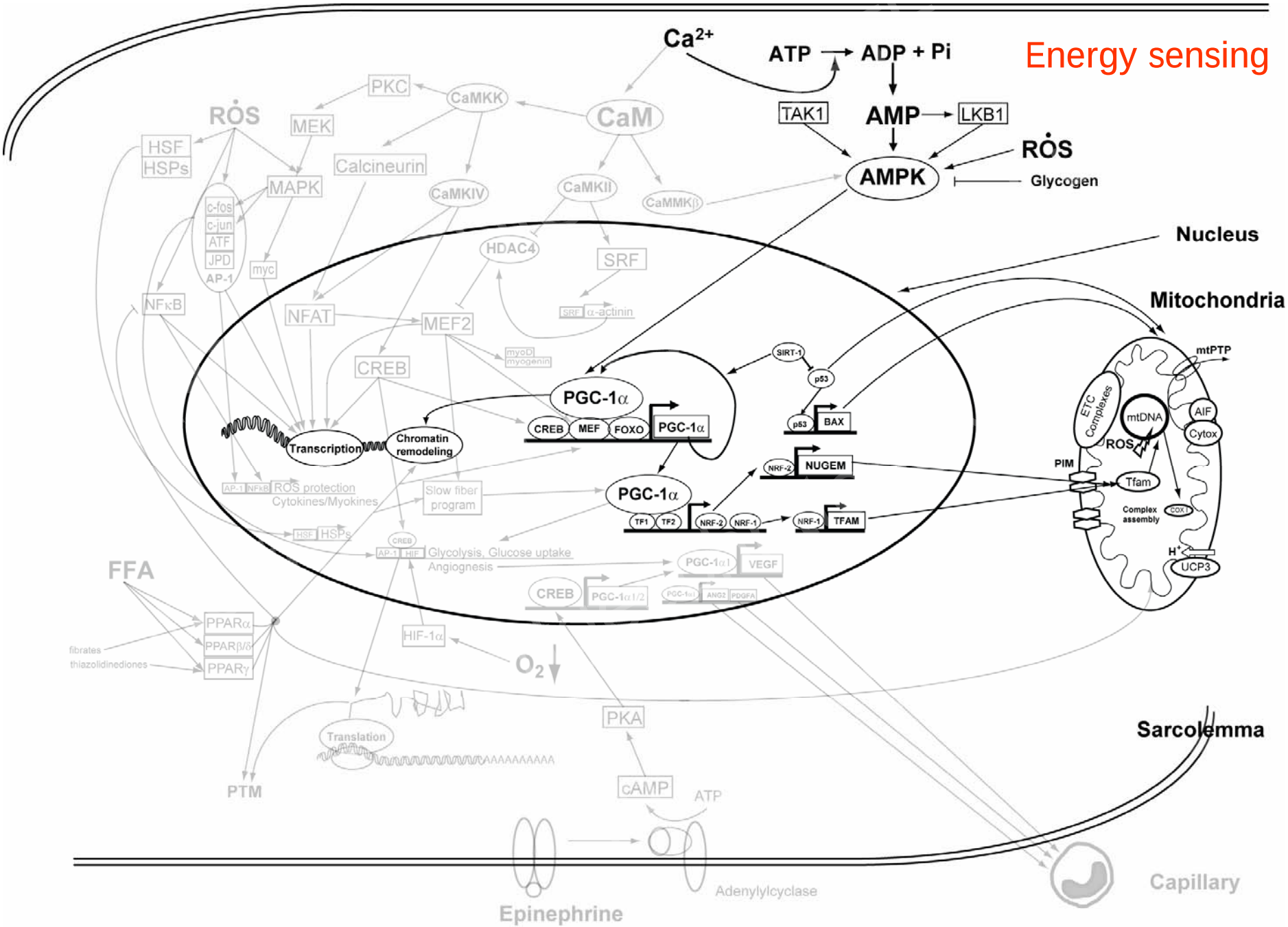
Adapted from Fluck 2003
Ther Umsch **60: 371-81**

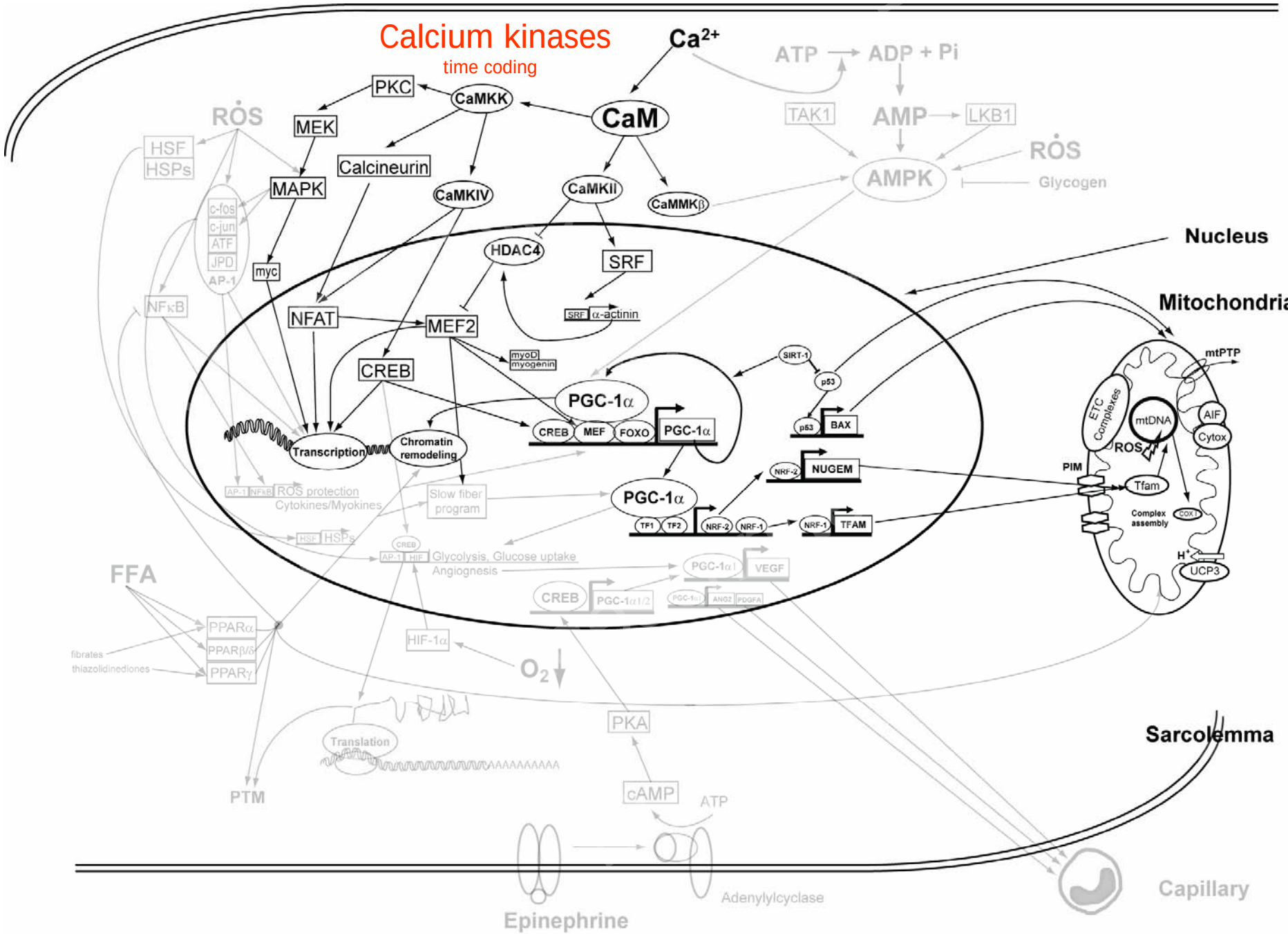


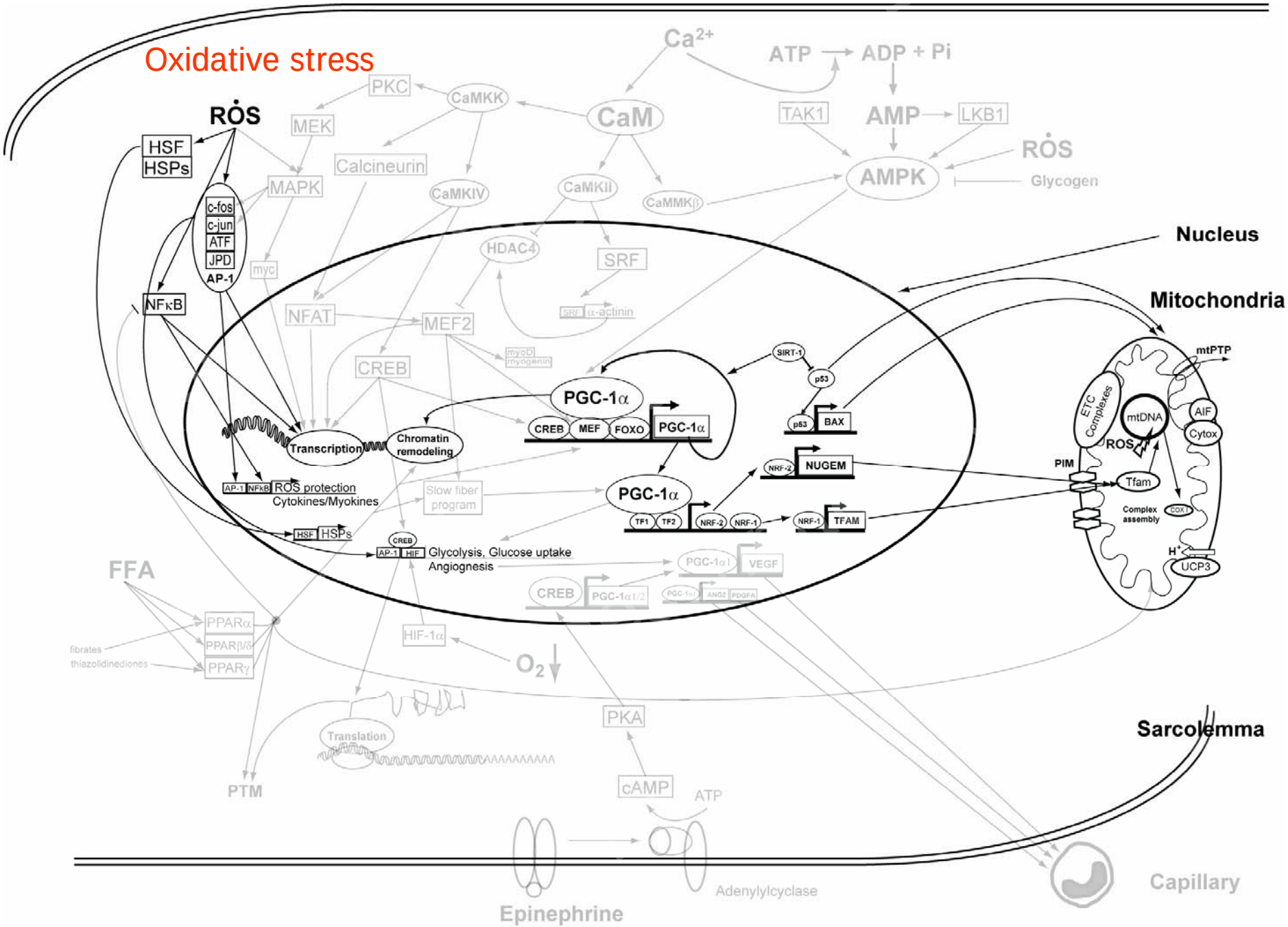
Endurance exercise training
qualitative changes – transcriptionally driven

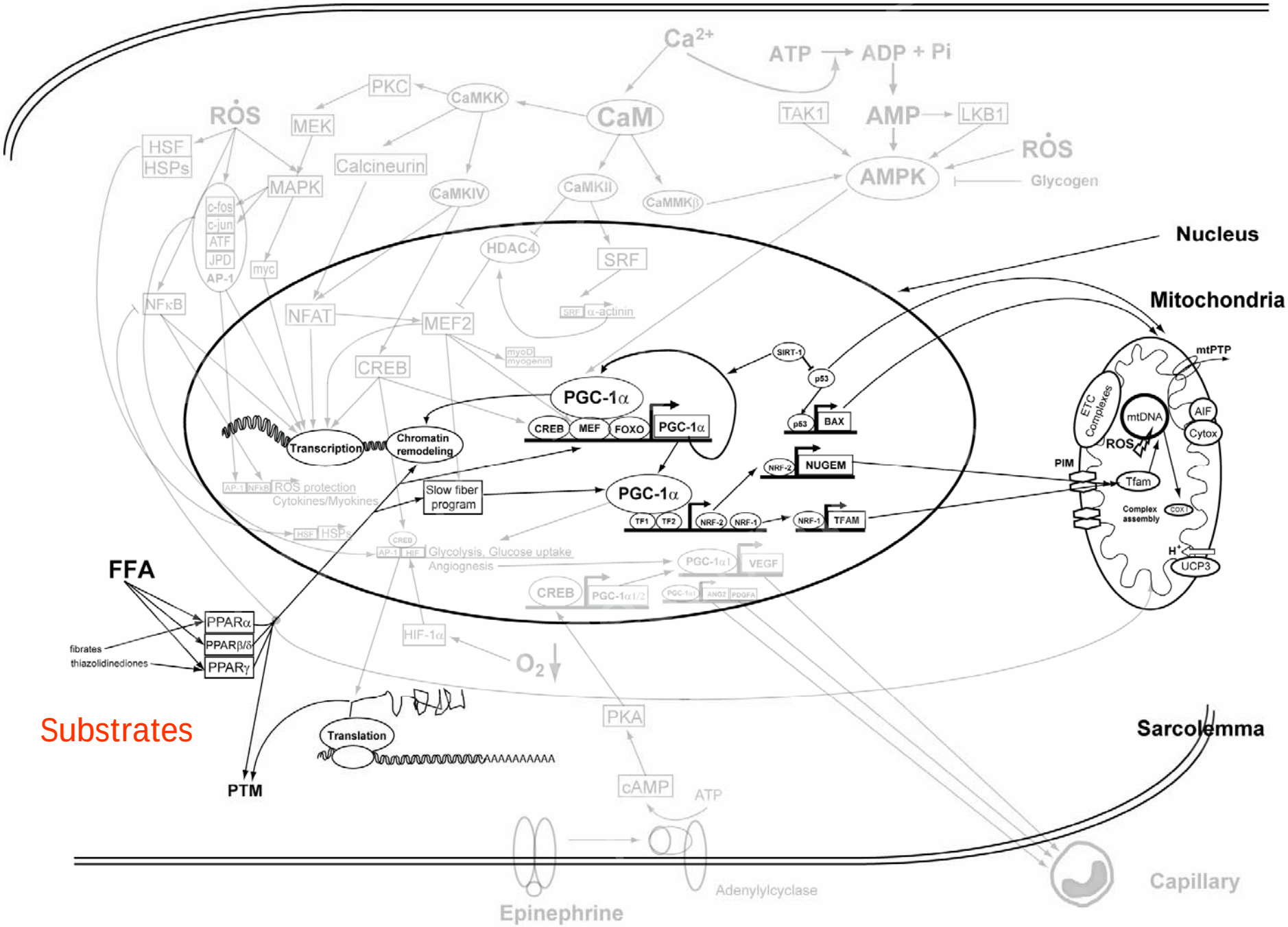
Hoppeler et al. Comprehensive Physiology 2011

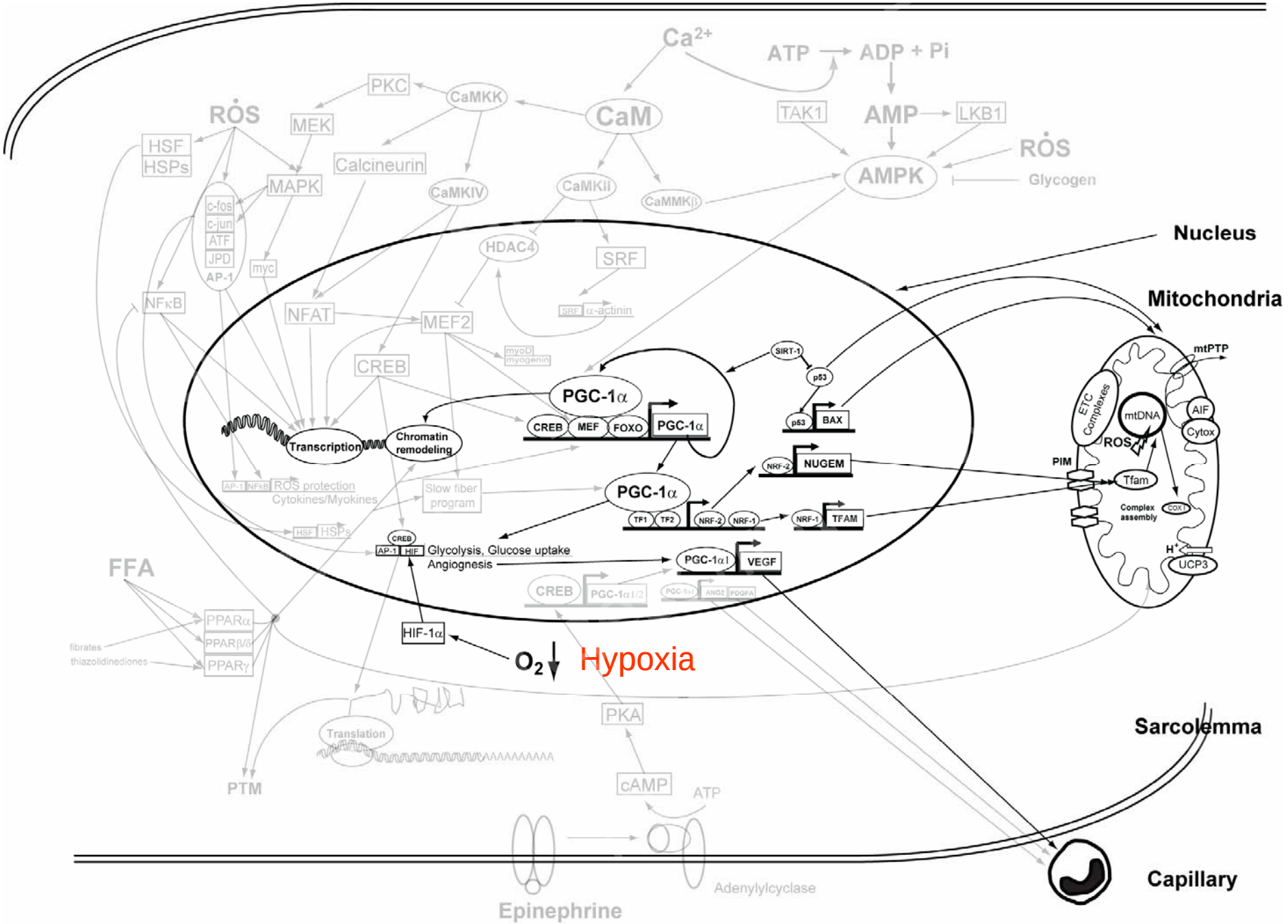
Energy sensing

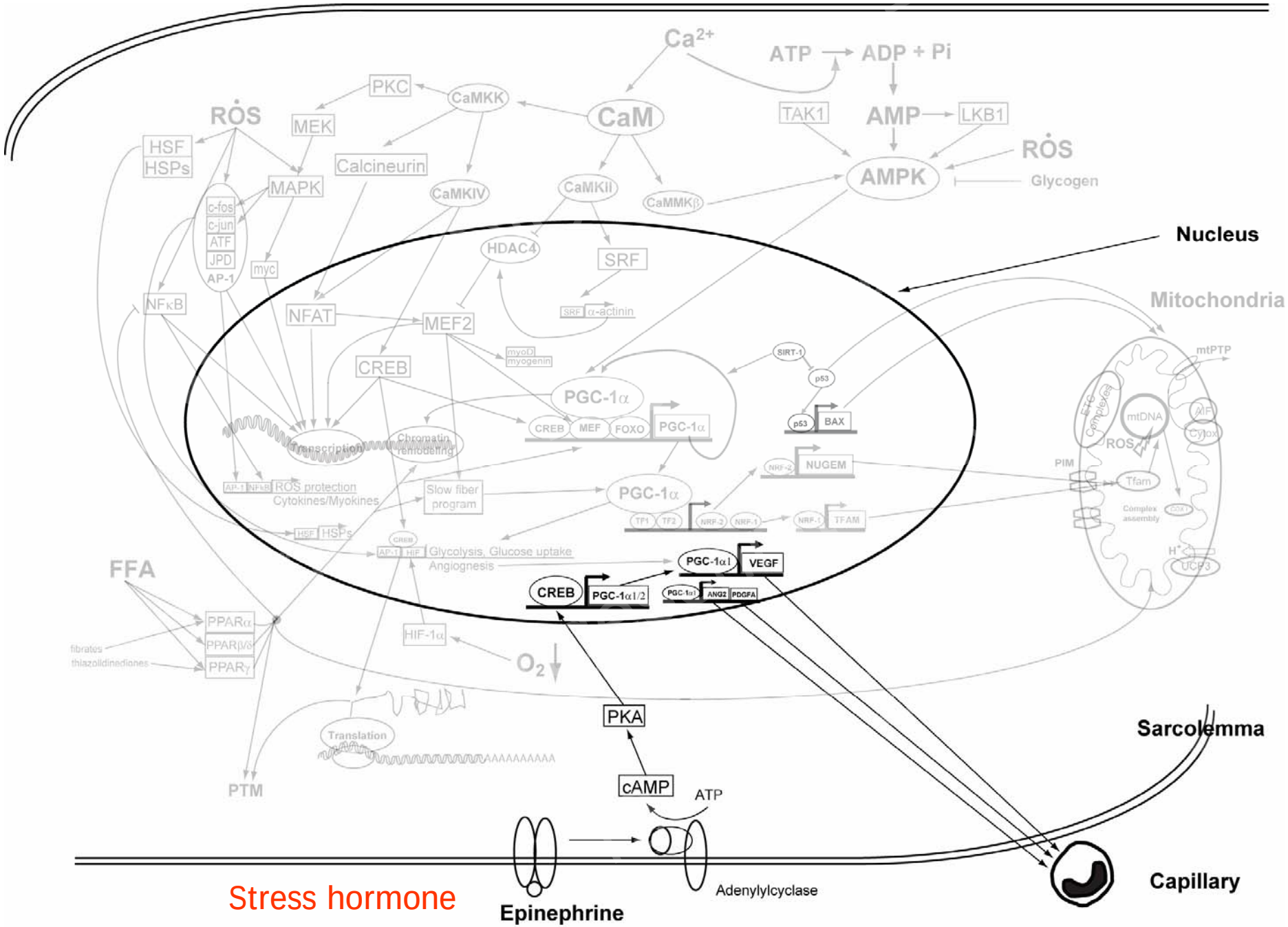


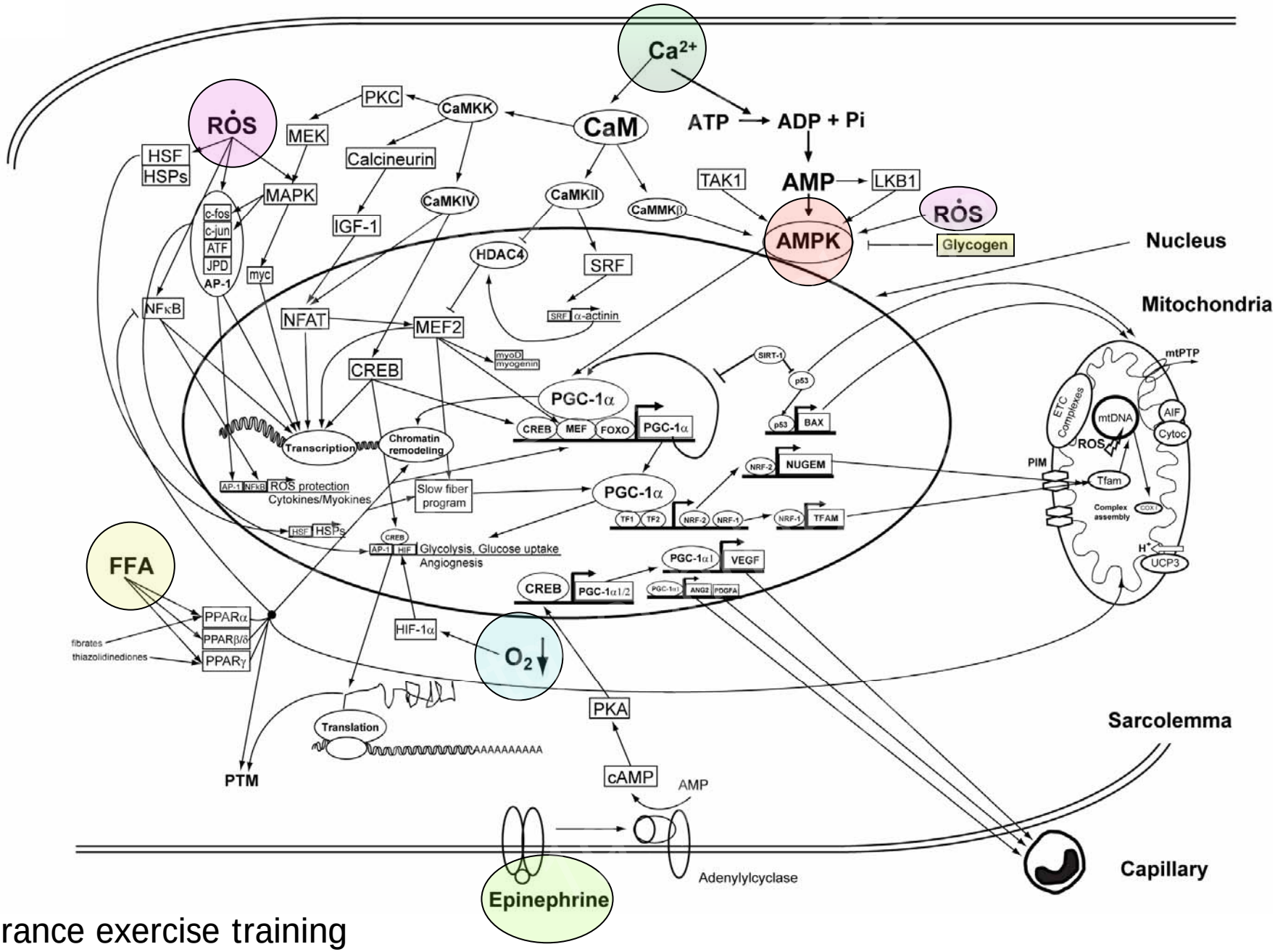

Calcium kinases
time coding
Ca2+
ATP
ADP + Pi
PKC
CaMKK
CaM
ROS
MEK
TAK1
AMP
LKB1
HSF
HSPs
Calcineurin
MAPK
CaMKIV
CaMKII
CaMMKβ
AMPK
ROS
Glycogen
c-fos
c-jun
ATF
JPD
AP-1
HDAC4
SRF
Nucleus
myc
NFκB
NFAT
MEF2
SRF
α-actinin
Mitochondria
myoD
myogenin
CREB
SIRT-1
p53
mtPTP
PGC-1α
CREB
MEF
FOXO
PGC-1α
p53
BAX
ETC Complexes
mtDNA
AIF
Cytox
Transcription
Chromatin remodeling
ROS
NRF-2
NUGEM
PIM
Tfam
AP-1
NFκB
ROS protection
Cytokines/Myokines
Slow fiber program
PGC-1α
TF1
TF2
NRF-2
NRF-1
NRF-1
TFAM
Complex assembly
COX I
HSF
HSPs
CREB
AP-1
HIF
Glycolysis, Glucose uptake
Angiogenesis
PGC-1α
VEGF
H+
UCP3
FFA
CREB
PGC-1α1/2
PPARα
PPARβ/δ
PPARγ
fibrates
thiazolidinediones
HIF-1α
O2
PKA
Translation
AAAAAAAAAA
Sarcolemma
PTM
cAMP
ATP
Adenylylcyclase
Epinephrine
Capillary


Oxidative stress
Ca2+
ATP
ADP + Pi
PKC
CaMKK
CaM
TAK1
AMP
LKB1
ROS
MEK
Calcineurin
AMPK
Glycogen
HSF
HSPs
MAPK
CaMKIV
CaMKII
CaMMKβ
c-fos
c-jun
ATF
JPD
AP-1
HDAC4
SRF
Nucleus
myc
NFκB
NFAT
MEF2
SRF
α-actinin
Mitochondria
myoD
myogenin
CREB
SIRT-1
p53
PGC-1α
mtPTP
CREB
MEF
FOXO
PGC-1α
p53
BAX
ETC Complexes
mtDNA
AIF
Cytox
Transcription
Chromatin remodeling
ROS
PIM
NRF-2
NUGEM
AP-1
NFκB
ROS protection
Cytokines/Myokines
Slow fiber program
Tfam
PGC-1α
TF1
TF2
NRF-2
NRF-1
NRF-1
TFAM
Complex assembly
COX I
HSF
HSPs
CREB
AP-1
HIF
Glycolysis, Glucose uptake
Angiogenesis
PGC-1α1
VEGF
H+
UCP3
FFA
CREB
PGC-1α1/2
PGC-1α1
ANG2
PDGFA
PPARα
PPARβ/δ
PPARγ
fibrates
thiazolidinediones
HIF-1α
O2
PKA
Translation
AAAAAAAAAA
Sarcolemma
PTM
cAMP
ATP
Adenylylcyclase
Epinephrine
Capillary


Substrates
FFA
fibrates
thiazolidinediones
PPARα
PPARβ/δ
PPARγ
PTM
Translation
AAAAAAAAAA
HIF-1α
O2
PKA
cAMP
ATP
Epinephrine
Adenylylcyclase
Capillary
Sarcolemma
Nucleus
Mitochondria
Ca2+
ATP
ADP + Pi
AMP
LKB1
TAK1
AMPK
ROS
Glycogen
CaM
CaMKK
CaMKII
CaMKIV
CaMMKβ
PKC
MEK
MAPK
Calcineurin
HSF
HSPs
c-fos
c-jun
ATF
JPD
AP-1
myc
NFκB
NFAT
MEF2
CREB
HDAC4
SRF
SRF α-actinin
myoD
myogenin
PGC-1α
CREB
MEF
FOXO
PGC-1α
Transcription
Chromatin remodeling
SIRT-1
p53
p53
BAX
NRF-2
NUGEM
PIM
Tfam
Slow fiber program
PGC-1α
TF1
TF2
NRF-2
NRF-1
NRF-1
TFAM
AP-1
NFκB
ROS protection
Cytokines/Myokines
HSF
HSPs
CREB
AP-1
HIF
Glycolysis, Glucose uptake
Angiogenesis
PGC-1α1
VEGF
CREB
PGC-1α1/2
PGC-1α1
ANG2
PDGFA
mtPTP
ETC Complexes
mtDNA
ROS
AIF
Cytox
Complex assembly
COX1
H+
UCP3


Ca2+
ATP
ADP + Pi
PKC
CaMKK
CaM
TAK1
AMP
LKB1
ROS
MEK
HSF
HSPs
Calcineurin
AMPK
Glycogen
MAPK
CaMKIV
CaMKII
CaMMKβ
c-fos
c-jun
ATF
JPD
AP-1
myc
HDAC4
SRF
Nucleus
NFκB
NFAT
MEF2
SRF α-actinin
Mitochondria
myoD
myogenin
CREB
SIRT-1
p53
PGC-1α
CREB MEF FOXO PGC-1α
p53 BAX
mtPTP
ETC Complexes
mtDNA
AIF
Cytox
ROS
Transcription
Chromatin remodeling
NRF-2 NUGEM
PIM
Tfam
AP-1 NFκB ROS protection
Cytokines/Myokines
Slow fiber program
PGC-1α
TF1 TF2 NRF-2 NRF-1
NRF-1 TFAM
Complex assembly
COX I
HSF HSPs
CREB
AP-1 HIF
Glycolysis, Glucose uptake
Angiogenesis
PGC-1α1 VEGF
H+
UCP3
FFA
CREB PGC-1α1/2
PPARα
PPARβ/δ
PPARγ
fibrates
thiazolidinediones
HIF-1α
O2
Hypoxia
PKA
Translation
AAAAAAAAAA
Sarcolemma
PTM
cAMP
ATP
Adenylylcyclase
Epinephrine
Capillary


Ca2+
ATP
ADP + Pi
PKC
CaMKK
CaM
TAK1
AMP
LKB1
ROS
MEK
HSF
HSPs
Calcineurin
AMPK
ROS
Glycogen
MAPK
CaMKIV
CaMKII
CaMMKβ
c-fos
c-jun
ATF
JPD
AP-1
myc
HDAC4
SRF
Nucleus
NFκB
NFAT
MEF2
SRF
α-actinin
Mitochondria
myoD
myogenin
CREB
SIRT-1
p53
PGC-1α
CREB
MEF
FOXO
PGC-1α
p53
BAX
mtPTP
mtDNA
AIF
Cytoc
ROS
Transcription
Chromatin remodeling
NRF-2
NUGEM
PIM
AP-1
NFκB
ROS protection
Cytokines/Myokines
Slow fiber program
PGC-1α
Tfam
TF1
TF2
NRF-2
NRF-1
NRF-1
TFAM
Complex assembly
HSF
HSPs
CREB
AP-1
HIF
Glycolysis, Glucose uptake
Angiogenesis
PGC-1α1
VEGF
FFA
CREB
PGC-1α1/2
PGC-1α1
ANG2
PDGFA
PPARα
PPARβ/δ
PPARγ
fibrates
thiazolidinediones
HIF-1α
O2
PKA
Translation
AAAAAAAAAA
Sarcolemma
PTM
cAMP
ATP
Stress hormone
Epinephrine
Adenylylcyclase
Capillary

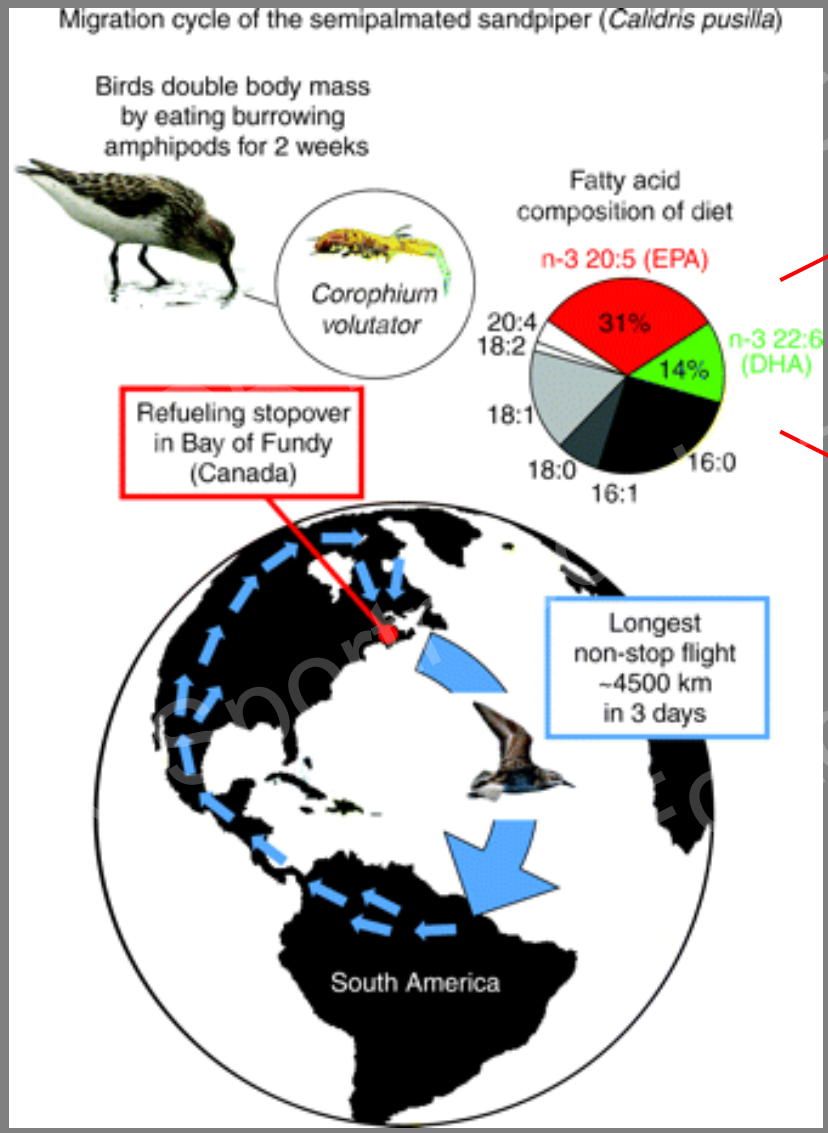


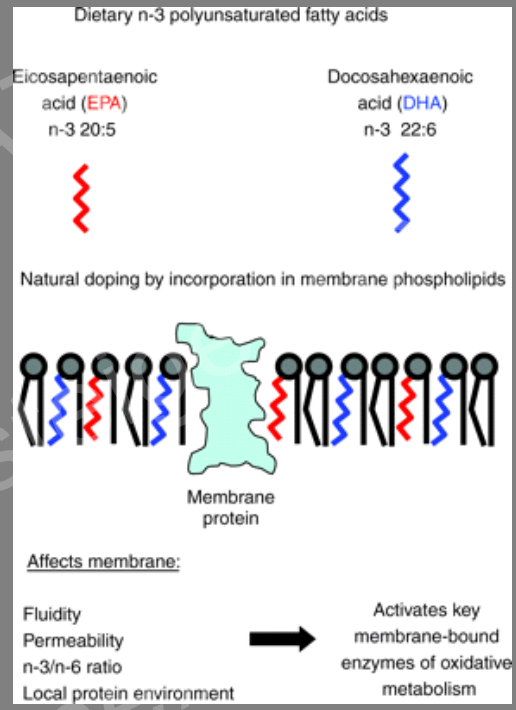
Endurance exercise training
qualitative changes – transcriptionally driven

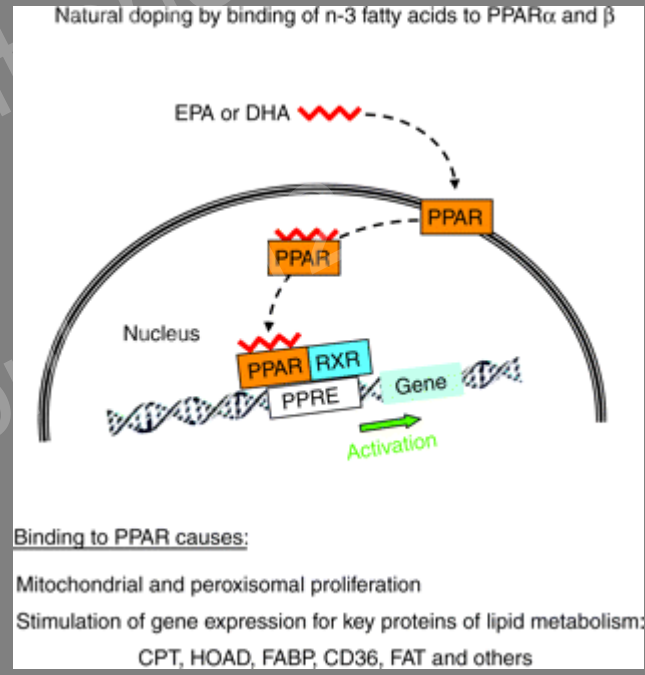
Hoppeler et al. Comprehensive Physiology 2011

The physiology of long-distance migration: extending the limits of endurance metabolism

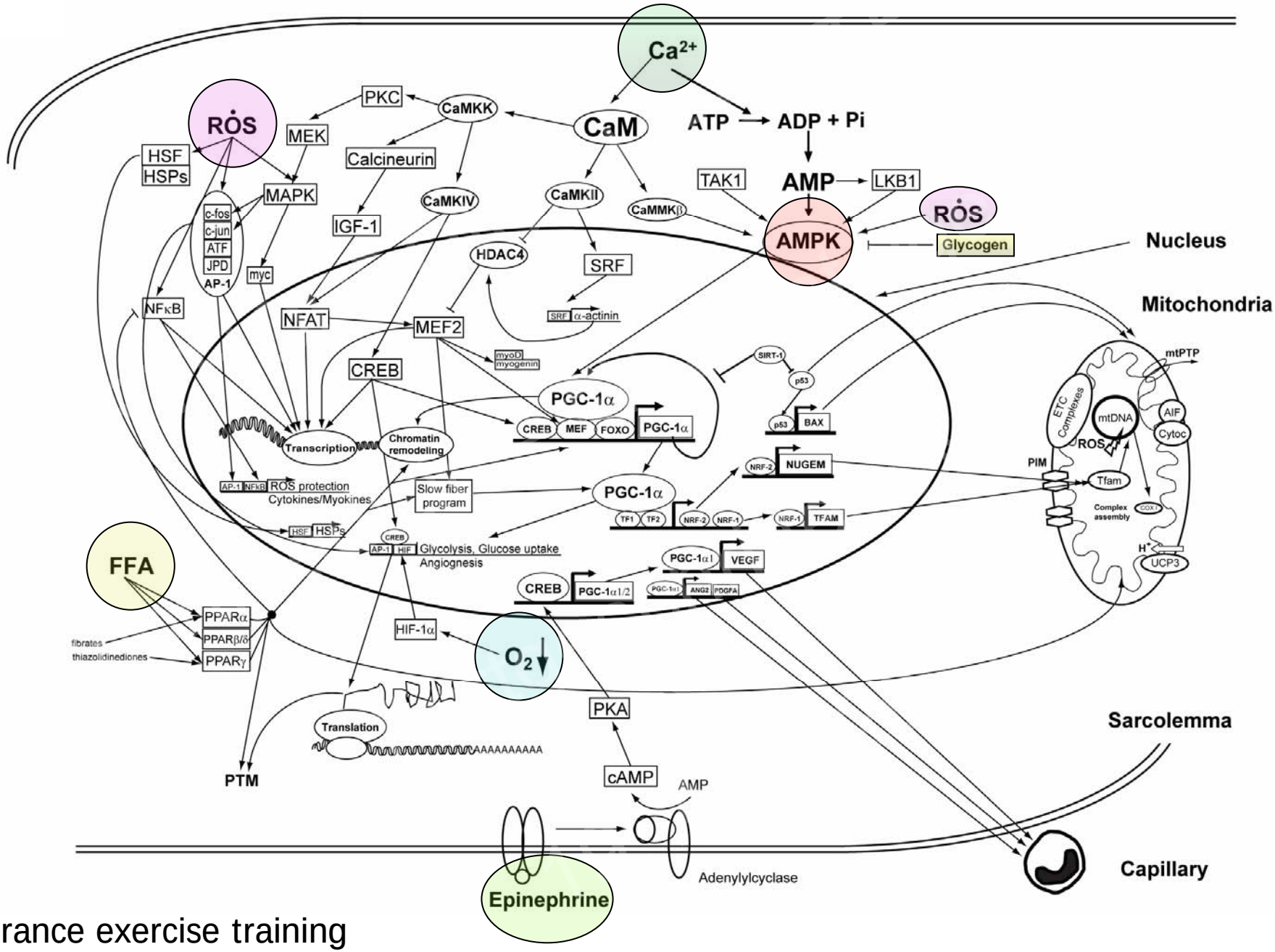
Weber J.-M.





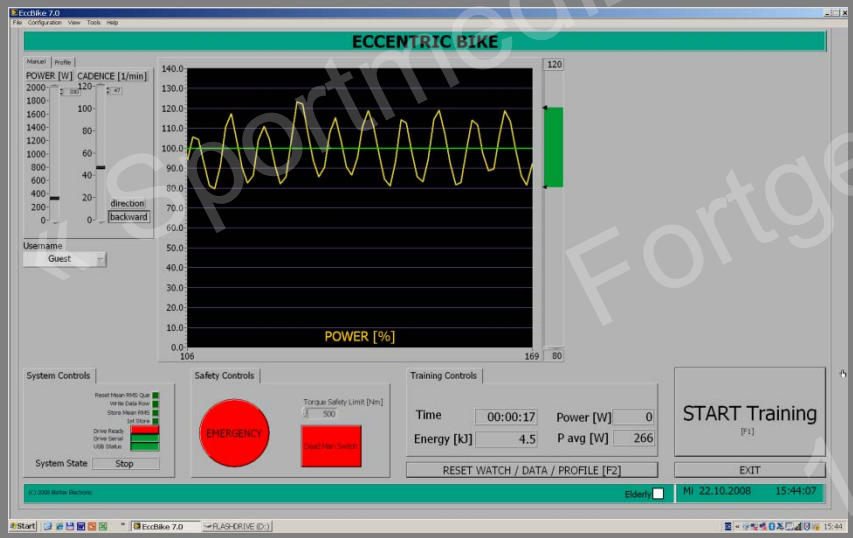


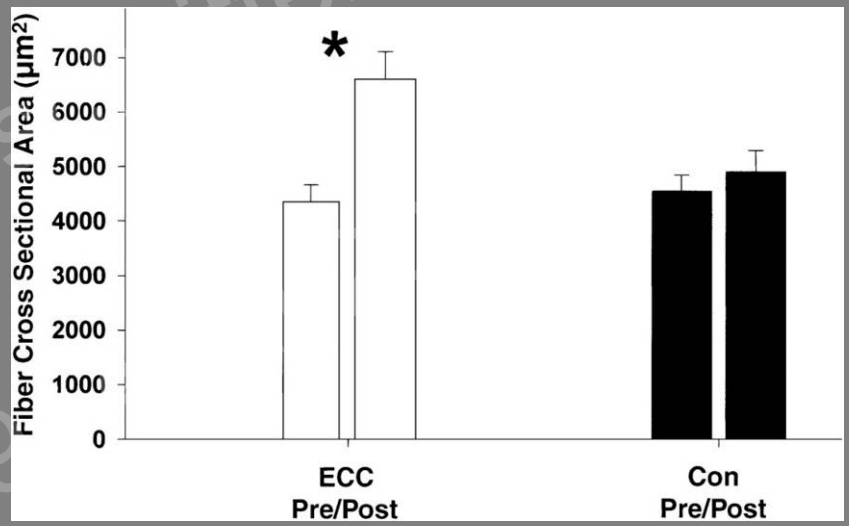
J Exp Biol. 2009 Mar;212(Pt 5):593-7



Endurance exercise training
qualitative changes – transcriptionally driven

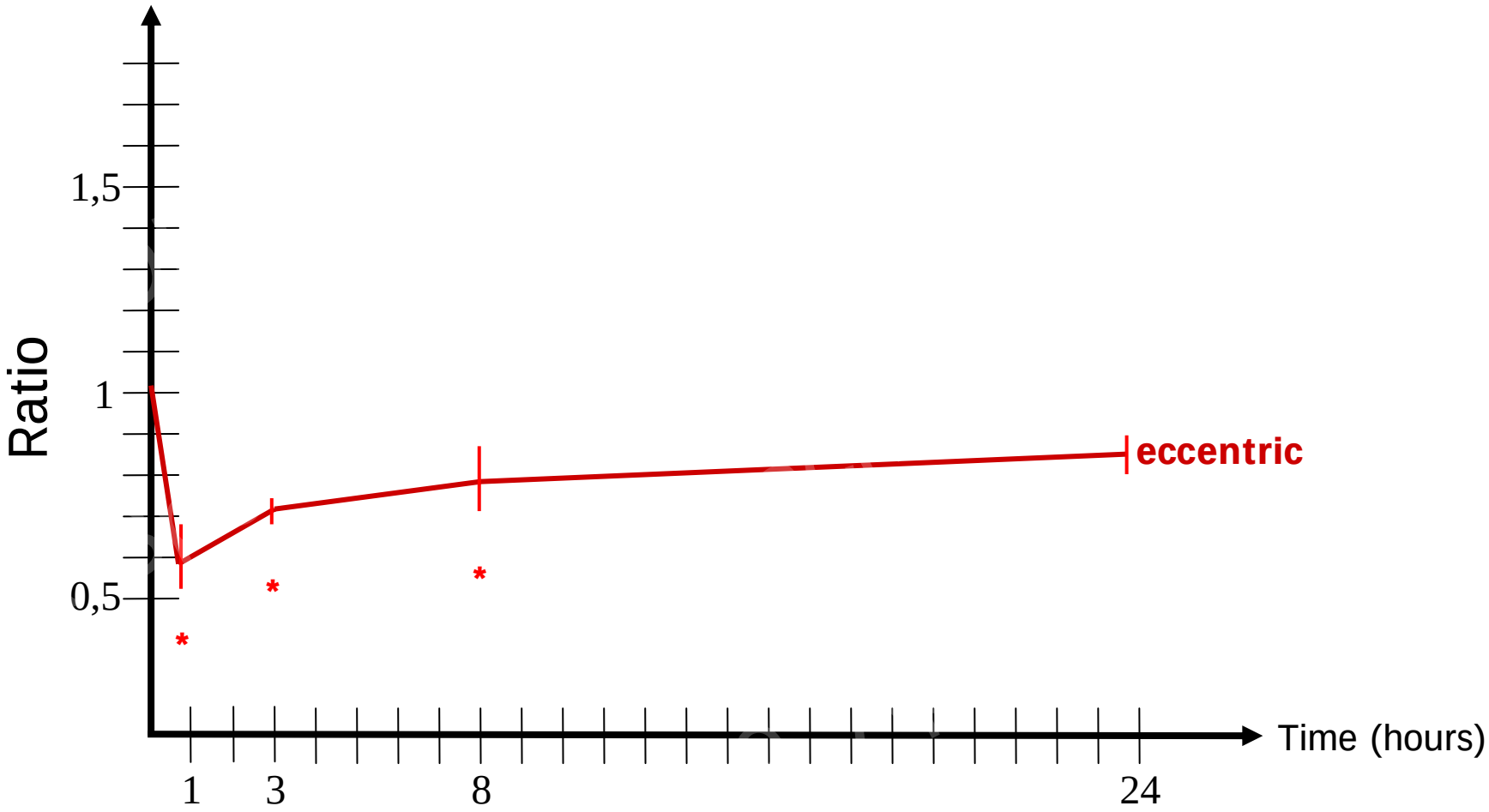
Hoppeler et al. Comprehensive Physiology 2011



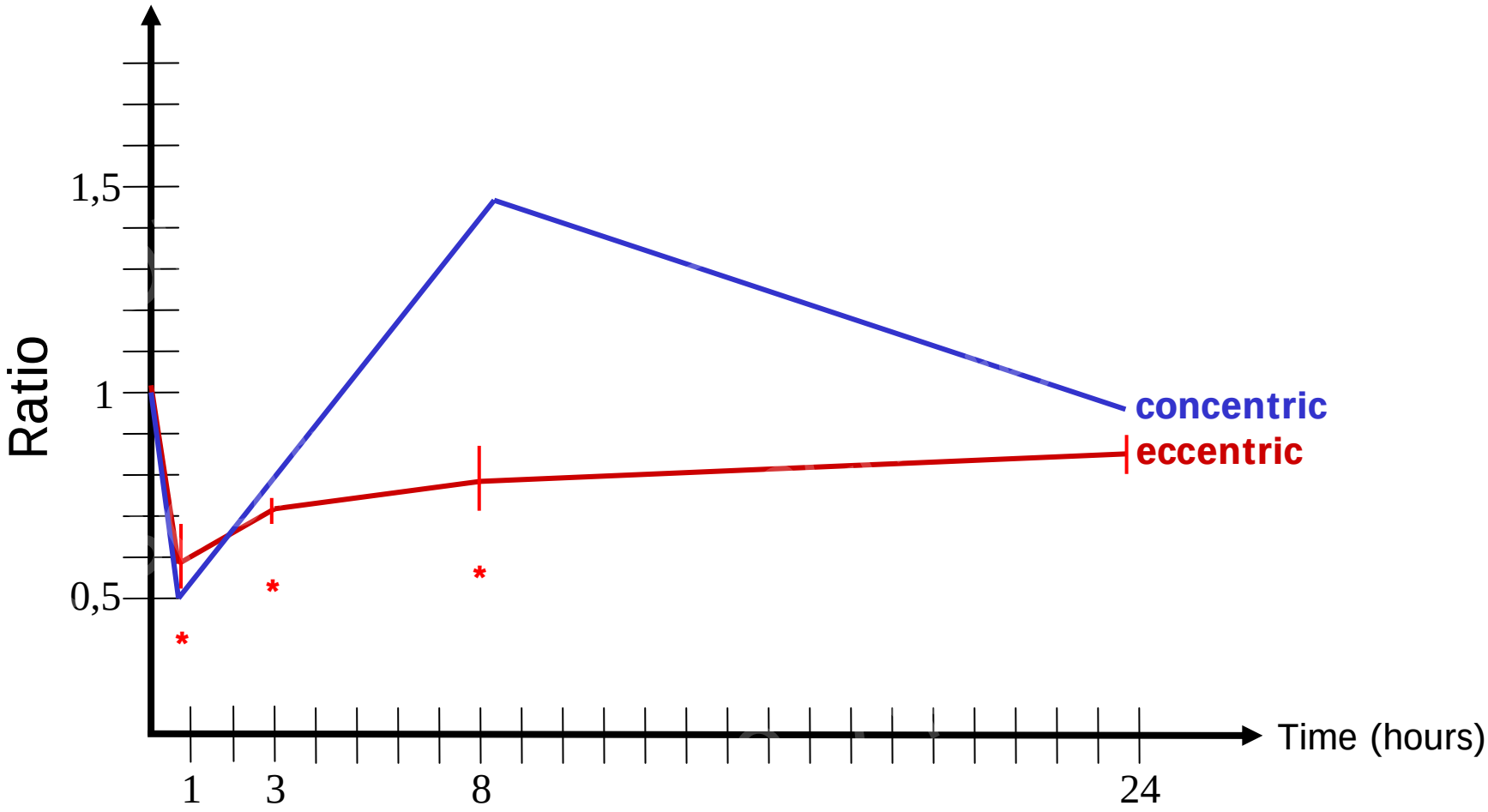


LaStayo et al. Amer. J. Physiol. 2000

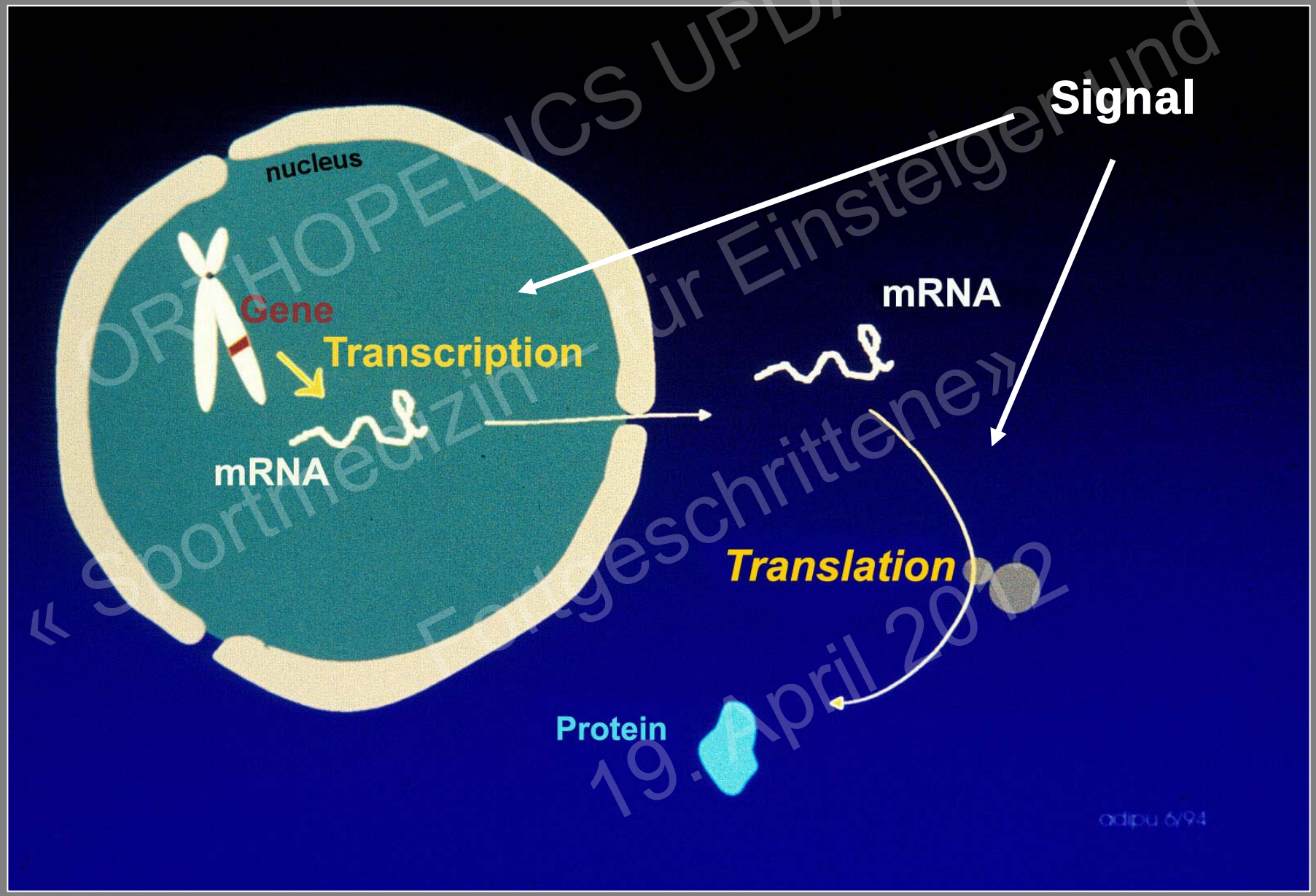
Response of muscle transcriptome after 30 min of eccentric exercise

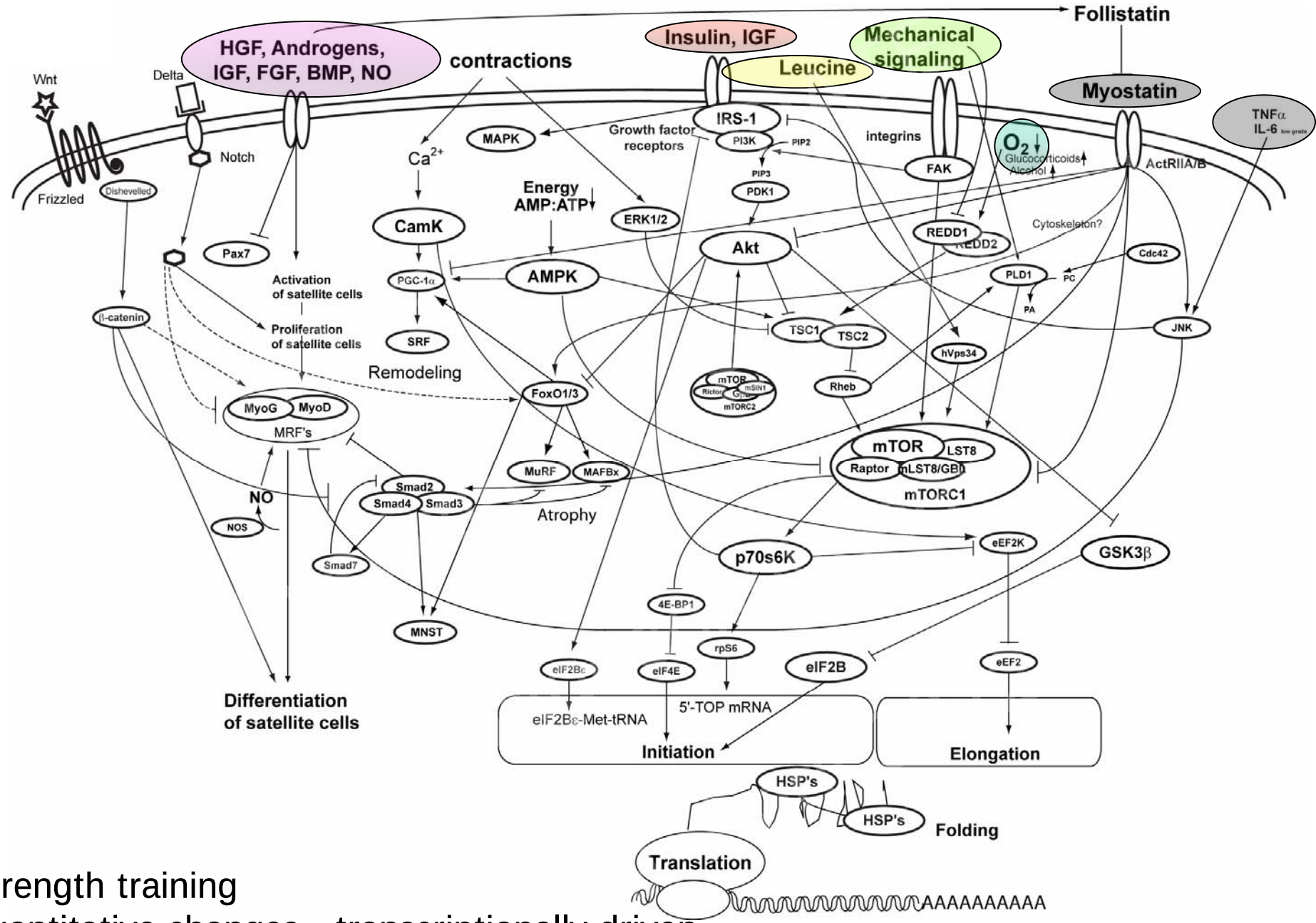


Time course of response of muscle transcriptome



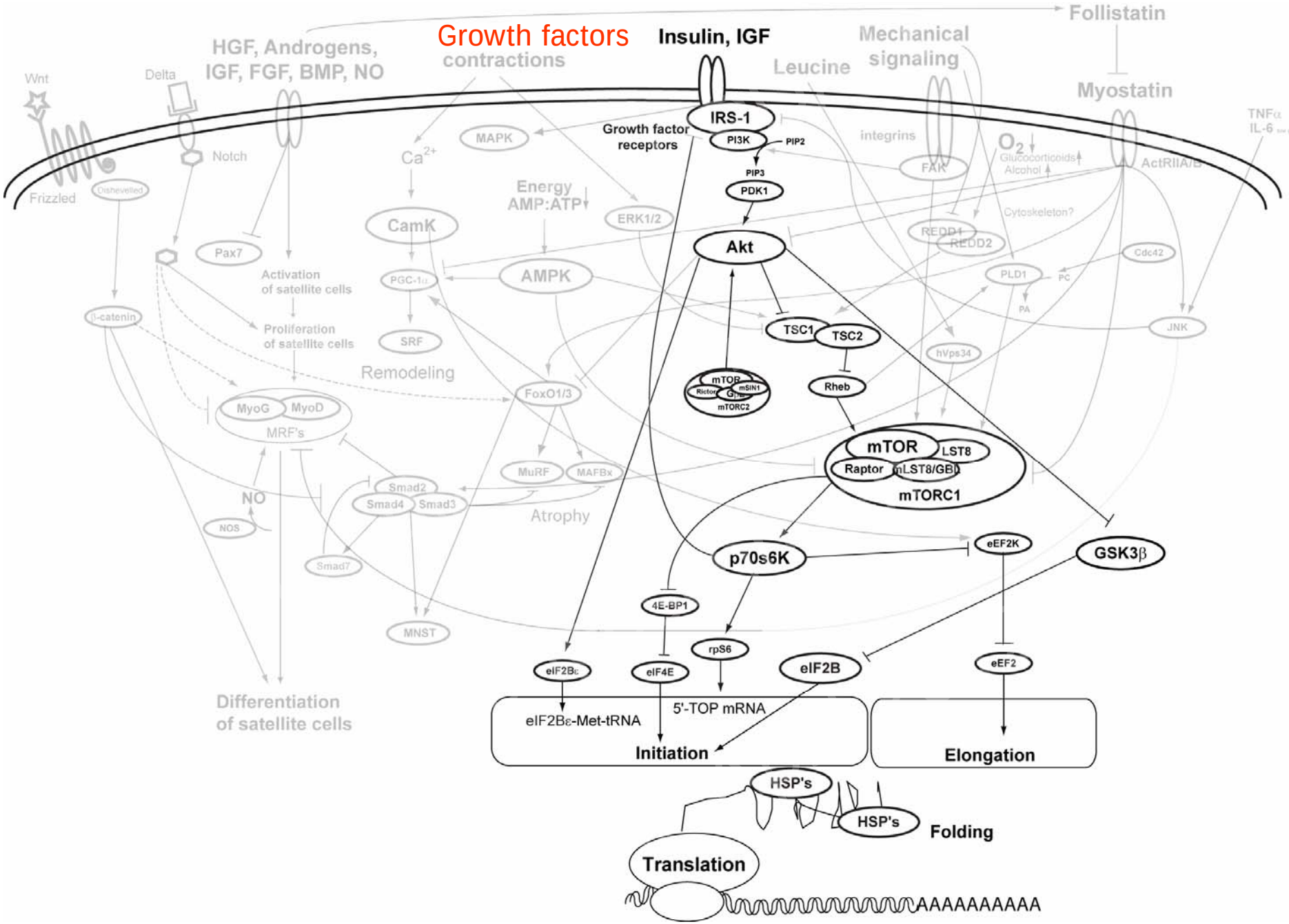
Mechanism of myofibrillar volume adjustement with exercise ?

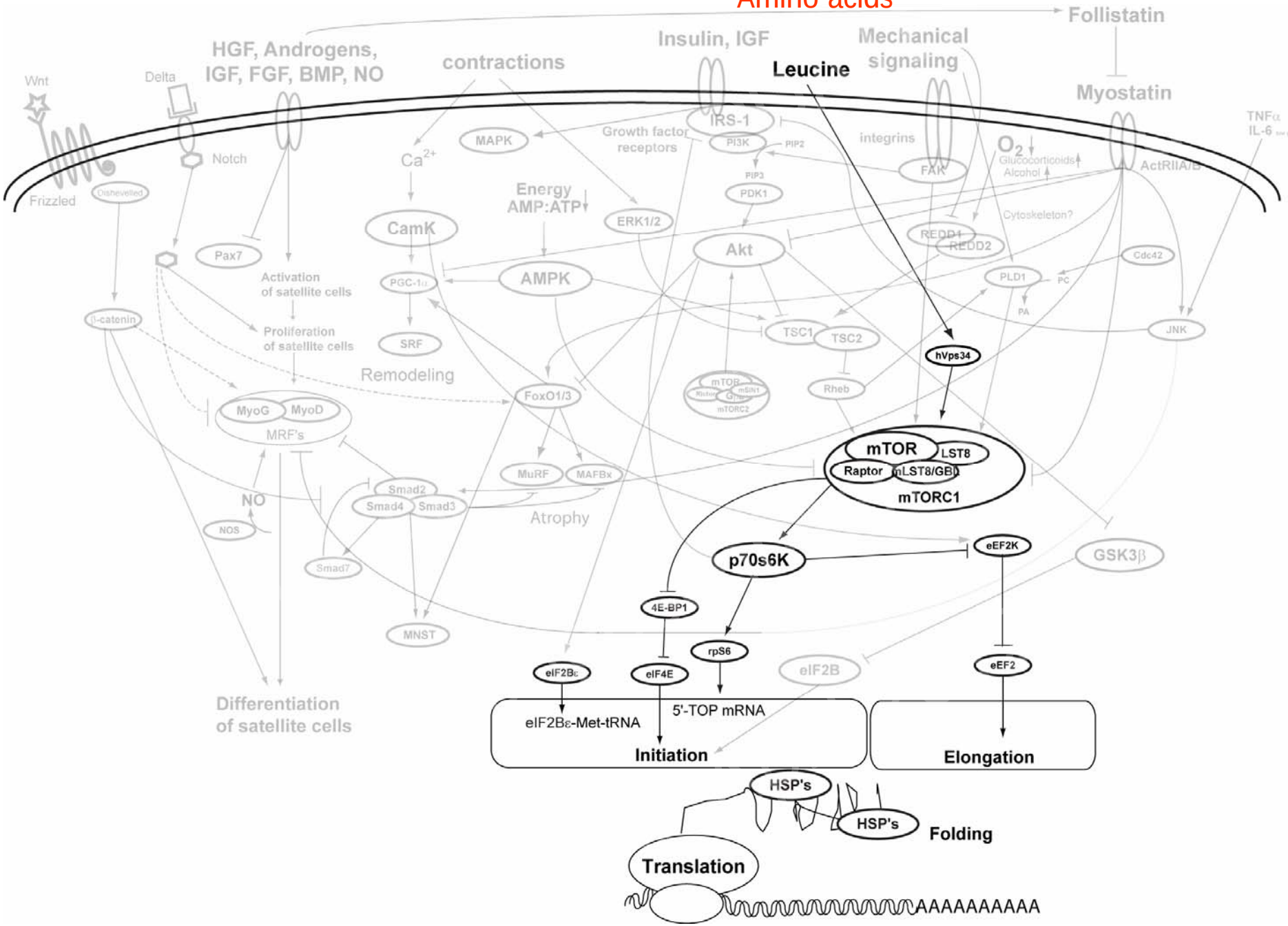


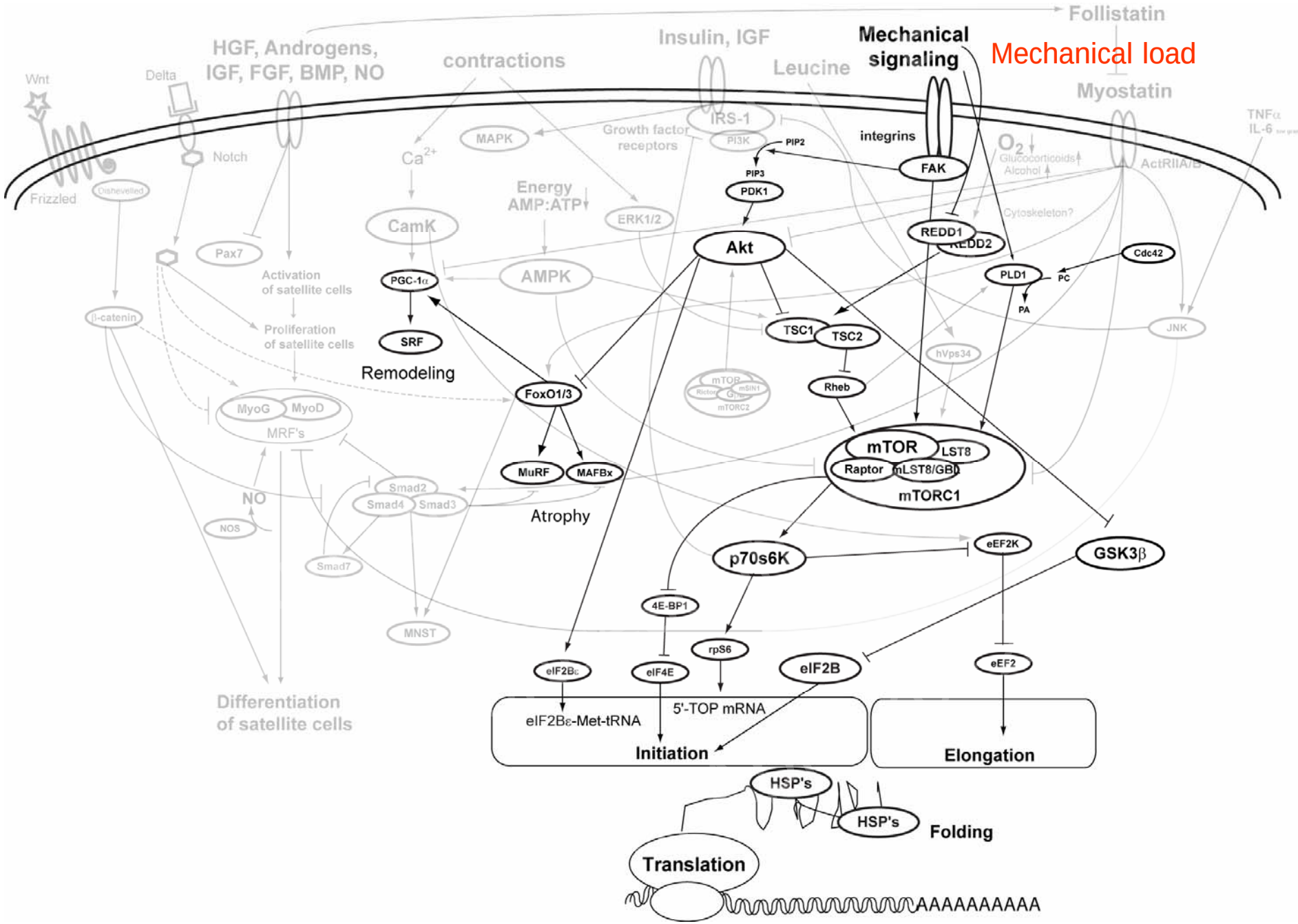


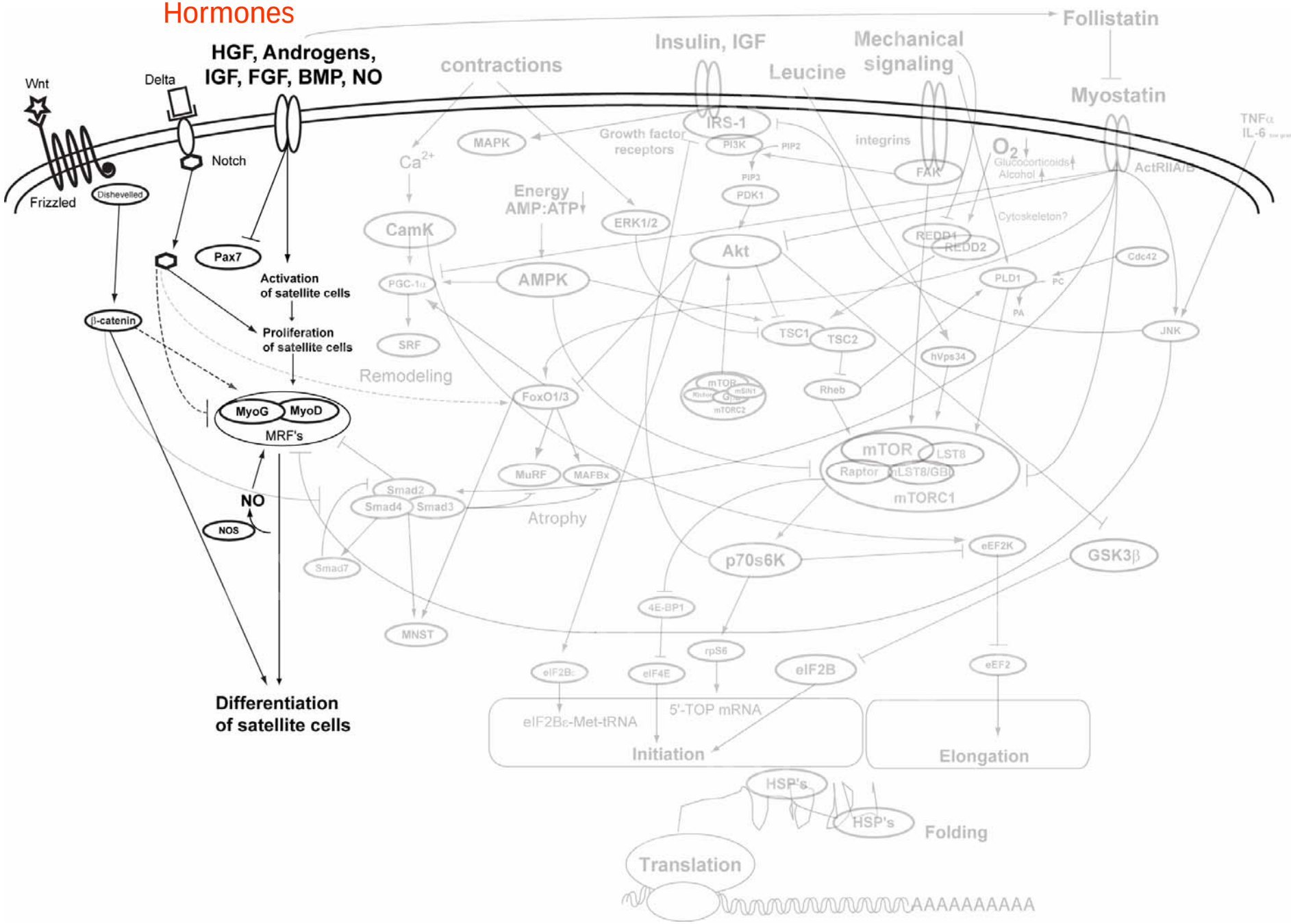
Strength training
quantitative changes - transcriptionally driven
plus reqruitment of DNA from stem cells

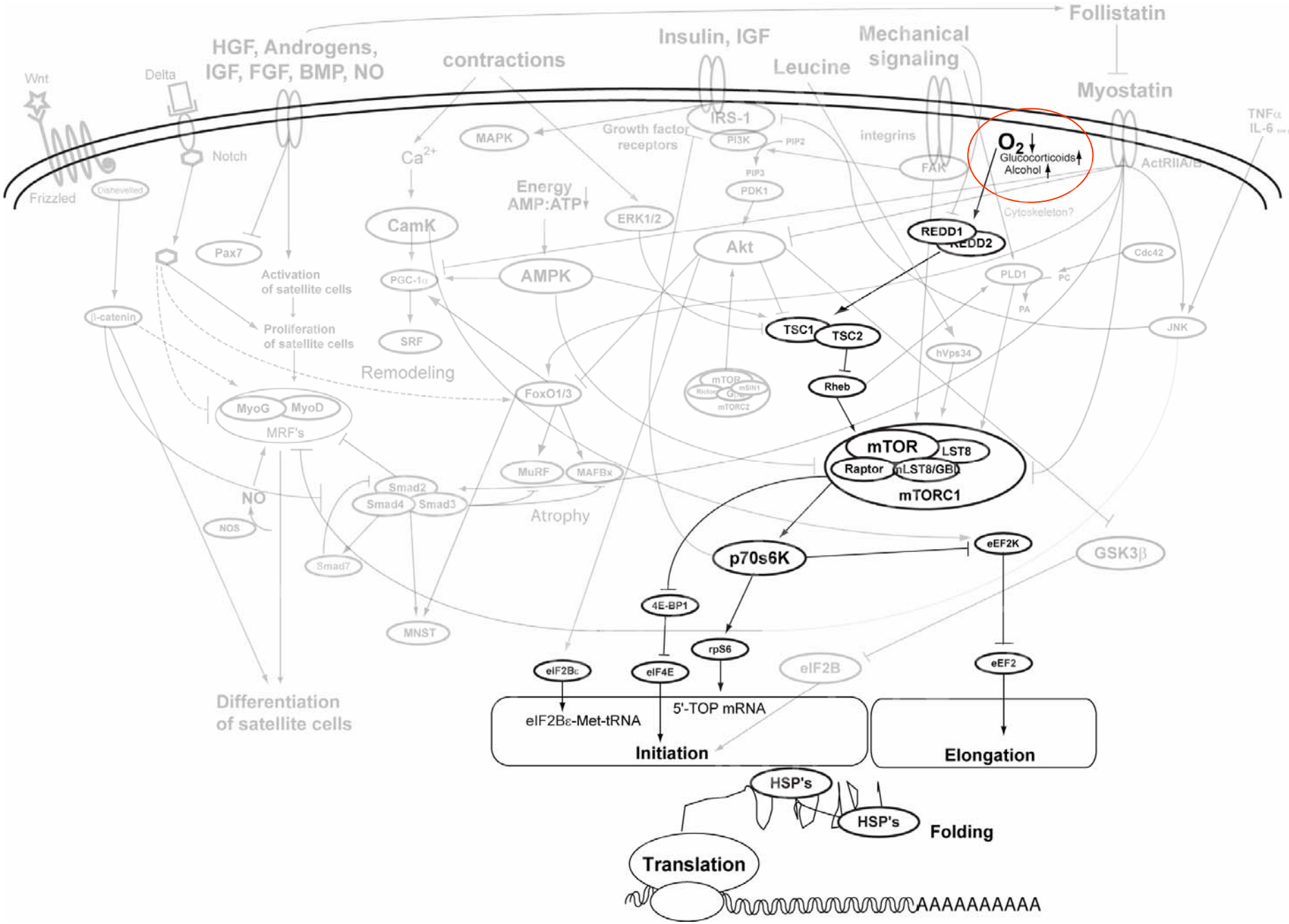
Hoppeler et al. Comprehensive Physiology 2011

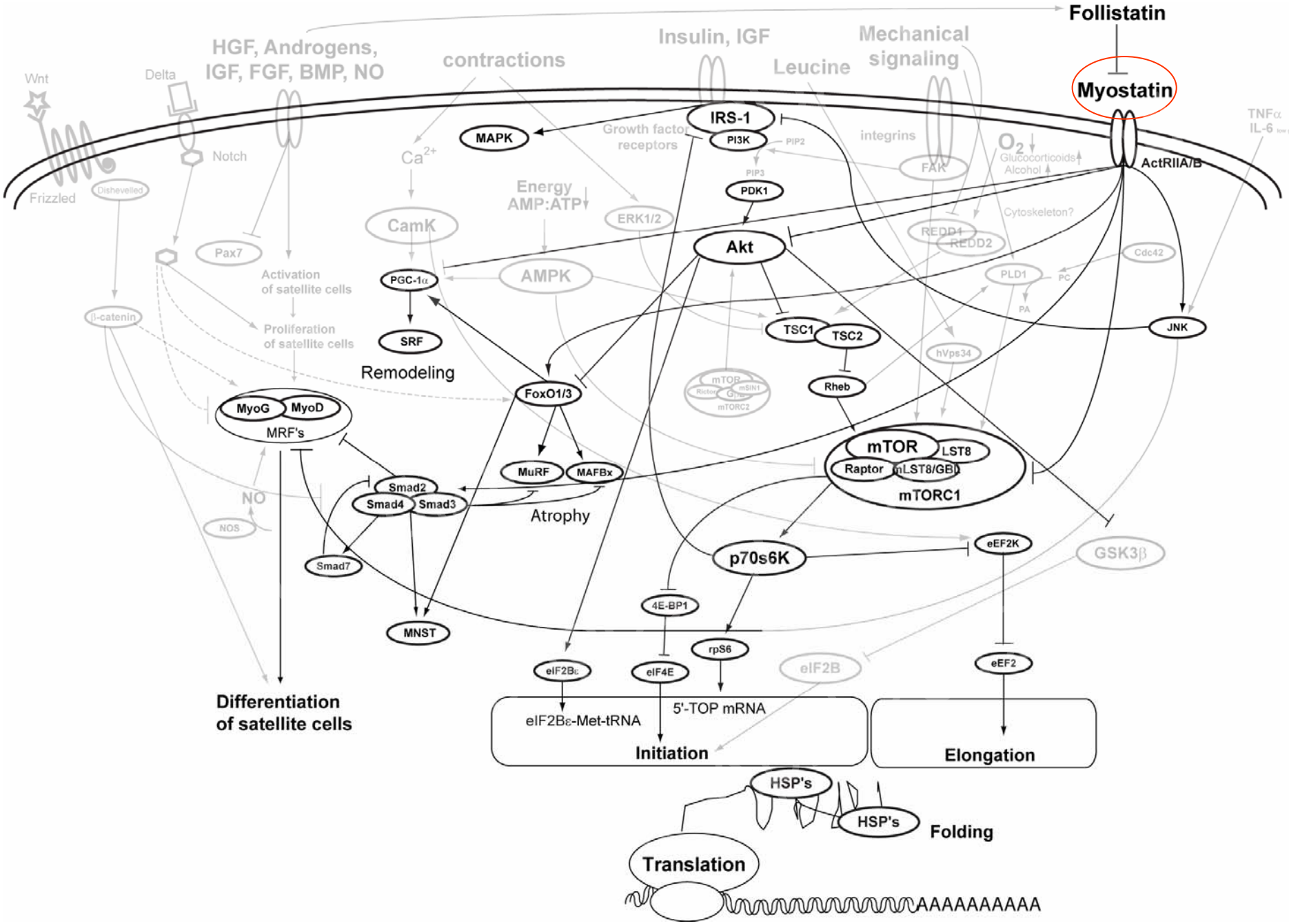

Growth factors
Follistatin
HGF, Androgens,
IGF, FGF, BMP, NO
contractions
Insulin, IGF
Mechanical
signaling
Leucine
Myostatin
Wnt
Delta
Notch
Frizzled
Dishevelled
Ca2+
MAPK
IRS-1
Growth factor
receptors
PI3K
PIP2
PIP3
PDK1
integrins
FAK
O2
Glucocorticoids
Alcohol
ActRIIA/B
TNFα
IL-6
Energy
AMP:ATP
ERK1/2
CamK
Akt
REDD1
REDD2
Cytoskeleton?
Cdc42
PLD1
PC
PA
JNK
Pax7
Activation
of satellite cells
PGC-1α
AMPK
β-catenin
Proliferation
of satellite cells
SRF
Remodeling
TSC1
TSC2
hVps34
mTOR
Rictor
mSIN1
mTORC2
Rheb
FoxO1/3
MyoG
MyoD
MRF's
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
MuRF
MAFBx
Smad2
Smad4
Smad3
Atrophy
NO
NOS
Smad7
p70s6K
eEF2K
GSK3β
4E-BP1
MNST
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
5'-TOP mRNA
eIF2Bε-Met-tRNA
Initiation
Elongation
Differentiation
of satellite cells
HSP's
HSP's
Folding
Translation
AAAAAAAAAA

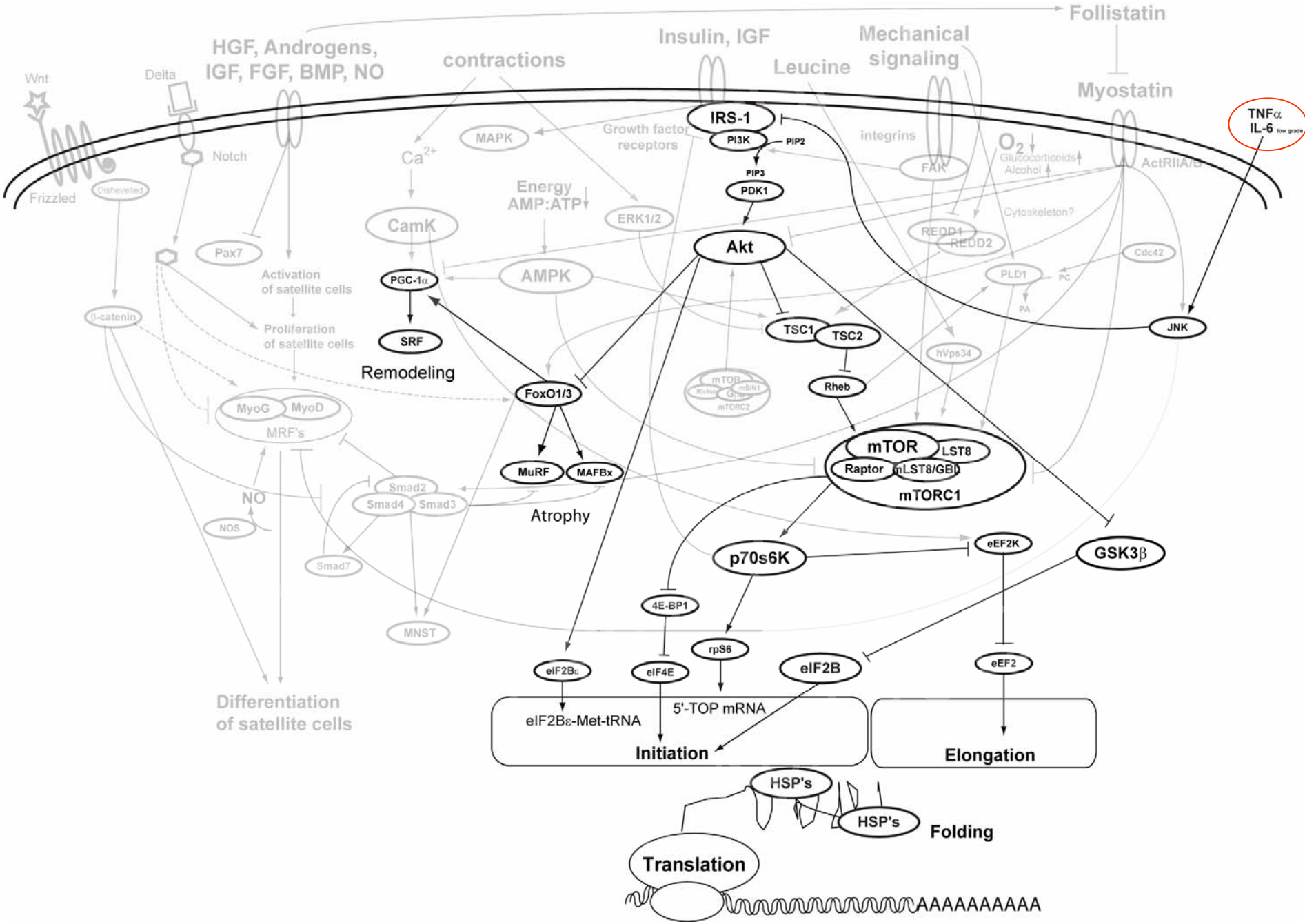

Amino acids
Follistatin
Myostatin
HGF, Androgens,
IGF, FGF, BMP, NO
contractions
Insulin, IGF
Mechanical
signaling
Leucine
Wnt
Delta
Notch
Frizzled
Dishevelled
Pax7
Activation
of satellite cells
Proliferation
of satellite cells
β-catenin
MyoG
MyoD
MRF's
Differentiation
of satellite cells
NO
NOS
Smad7
Smad2
Smad4
Smad3
Atrophy
MuRF
MAFBx
MNST
Remodeling
SRF
PGC-1α
CamK
Ca2+
MAPK
ERK1/2
Energy
AMP:ATP
AMPK
FoxO1/3
IRS-1
PI3K
PIP2
PIP3
PDK1
Growth factor
receptors
Akt
integrins
FAK
O2
Glucocorticoids
Alcohol
Cytoskeleton?
REDD1
REDD2
TSC1
TSC2
Rheb
mTOR
mSin1
Rictor
Gβ
mTORC2
hVps34
PLD1
PC
PA
Cdc42
JNK
TNFα
IL-6
ActRIIA/B
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
p70s6K
eEF2K
GSK3β
4E-BP1
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
5'-TOP mRNA
eIF2Bε-Met-tRNA
Initiation
Elongation
HSP's
HSP's
Folding
Translation
AAAAAAAAAA

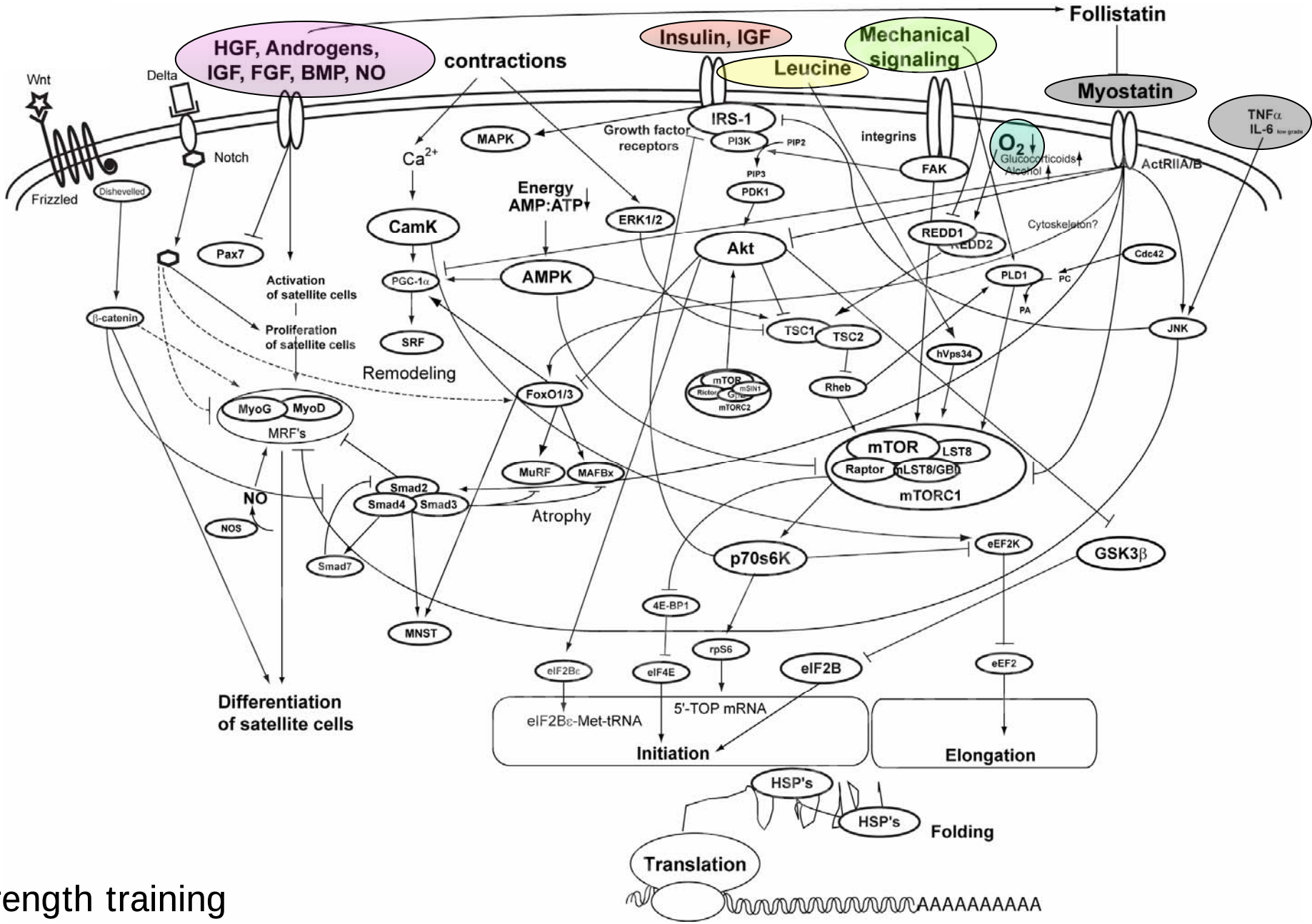

Follistatin
Mechanical load
Mechanical signaling
Insulin, IGF
HGF, Androgens, IGF, FGF, BMP, NO
contractions
Leucine
Myostatin
Wnt
Delta
Notch
Frizzled
Dishevelled
integrins
FAK
IRS-1
PI3K
PIP2
PIP3
PDK1
MAPK
Growth factor receptors
Ca2+
CamK
Energy AMP:ATP
ERK1/2
Akt
REDD1
REDD2
Cytoskeleton?
Glucocorticoids
Alcohol
ActRIIA/B
TNFα
IL-6
Cdc42
PLD1
PC
PA
JNK
Pax7
Activation of satellite cells
Proliferation of satellite cells
PGC-1α
AMPK
SRF
Remodeling
β-catenin
TSC1
TSC2
hVps34
Rheb
FoxO1/3
mTOR
Rictor
mSIN1
mTORC2
MyoG
MyoD
MRF's
MuRF
MAFBx
Atrophy
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
Smad2
Smad4
Smad3
NO
NOS
Smad7
MNST
p70s6K
eEF2K
GSK3β
4E-BP1
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
5'-TOP mRNA
eIF2Bε-Met-tRNA
Initiation
Elongation
Differentiation of satellite cells
HSP's
HSP's
Folding
Translation
AAAAAAAAAA


Hormones
HGF, Androgens,
IGF, FGF, BMP, NO
Wnt
Delta
Notch
Frizzled
Dishevelled
β-catenin
Pax7
Activation
of satellite cells
Proliferation
of satellite cells
Remodeling
MyoG
MyoD
MRF's
NO
NOS
Differentiation
of satellite cells
contractions
Insulin, IGF
Leucine
Mechanical
signaling
Follistatin
Myostatin
TNFα
IL-6
IRS-1
PI3K
PIP2
PIP3
PDK1
Growth factor
receptors
integrins
FAK
O2
Glucocorticoids
Alcohol
ActRIIA/B
MAPK
Ca2+
CamK
Energy
AMP:ATP
ERK1/2
Akt
AMPK
PGC-1α
SRF
REDD1
REDD2
Cytoskeleton?
Cdc42
PLD1
PC
PA
JNK
TSC1
TSC2
Rheb
hVps34
mTOR
mSIN1
Rictor
G
mTORC2
FoxO1/3
MuRF
MAFBx
Atrophy
Smad2
Smad4
Smad3
Smad7
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
p70s6K
eEF2K
GSK3β
4E-BP1
MNST
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
eIF2Bε-Met-tRNA
5'-TOP mRNA
Initiation
Elongation
HSP's
HSP's
Folding
Translation
AAAAAAAAAA


Follistatin
HGF, Androgens,
IGF, FGF, BMP, NO
contractions
Insulin, IGF
Leucine
Mechanical
signaling
Myostatin
Wnt
Delta
Notch
Frizzled
Dishevelled
MAPK
IRS-1
Growth factor
receptors
PI3K
PIP2
PIP3
integrins
FAK
O_2
Glucocorticoids
Alcohol
ActRIIA/B
TNFα
IL-6
Ca^{2+}
Energy
AMP:ATP
PDK1
ERK1/2
CamK
Pax7
Akt
REDD1
REDD2
Cytoskeleton?
Cdc42
PLD1
PC
PA
Activation
of satellite cells
AMPK
PGC-1α
β-catenin
Proliferation
of satellite cells
SRF
Remodeling
TSC1
TSC2
JNK
hVps34
mTOR
Rictor
mSIN1
mTORC2
Rheb
FoxO1/3
MyoG
MyoD
MRF's
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
MuRF
MAFBx
Smad2
Smad4
Smad3
Atrophy
NO
NOS
Smad7
p70s6K
eEF2K
GSK3β
4E-BP1
MNST
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
Differentiation
of satellite cells
eIF2Bε-Met-tRNA
5'-TOP mRNA
Initiation
Elongation
HSP's
HSP's
Folding
Translation
AAAAAAAAAA


Follistatin
Myostatin
ActRIIA/B
HGF, Androgens,
IGF, FGF, BMP, NO
contractions
Insulin, IGF
Leucine
Mechanical
signaling
Wnt
Delta
Notch
Frizzled
Dishevelled
Pax7
Activation
of satellite cells
Proliferation
of satellite cells
β-catenin
MyoG
MyoD
MRF's
Differentiation
of satellite cells
NO
NOS
Smad2
Smad4
Smad3
Smad7
MNST
Atrophy
MuRF
MAFBx
FoxO1/3
SRF
PGC-1α
Remodeling
CamK
Ca2+
AMPK
Energy
AMP:ATP
MAPK
ERK1/2
IRS-1
PI3K
PIP2
PIP3
PDK1
Akt
Growth factor
receptors
integrins
FAK
O2
Glucocorticoids
Alcohol
Cytoskeleton?
REDD1
REDD2
Cdc42
PLD1
PC
PA
JNK
TNFα
IL-6
TSC1
TSC2
Rheb
hVps34
mTOR
Rictor
mSIN1
mTORC2
mTOR
LST8
Raptor
mLST8/GBL
mTORC1
p70s6K
eEF2K
GSK3β
4E-BP1
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
eIF2Bε-Met-tRNA
5'-TOP mRNA
Initiation
Elongation
HSP's
HSP's
Folding
Translation
AAAAAAAAAA

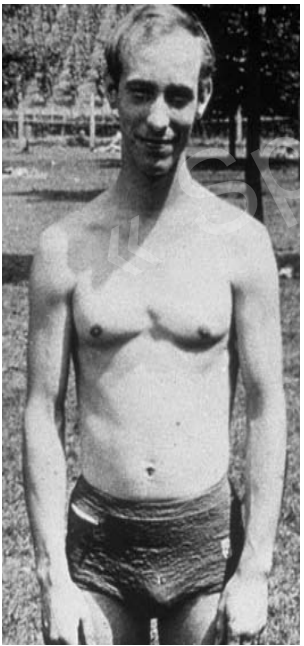

Follistatin
HGF, Androgens,
IGF, FGF, BMP, NO
contractions
Insulin, IGF
Mechanical
signaling
Leucine
Myostatin
Wnt
Delta
Notch
Frizzled
Dishevelled
IRS-1
PI3K
PIP2
PIP3
PDK1
MAPK
Growth factor
receptors
integrins
FAK
O_2
Glucocorticoids
Alcohol
ActRIIA/B
TNFα
IL-6
Ca^{2+}
Energy
AMP:ATP
ERK1/2
CamK
Akt
Cytoskeleton?
REDD1
REDD2
Cdc42
PLD1
PC
PA
Pax7
Activation
of satellite cells
Proliferation
of satellite cells
PGC-1α
AMPK
β-catenin
SRF
Remodeling
TSC1
TSC2
JNK
hVps34
mTOR
mSin1
Rictor
G-protein
mTORC2
FoxO1/3
Rheb
MyoG
MyoD
MRF's
mTOR
LST8
Raptor
mLST8/GβL
mTORC1
MuRF
MAFBx
Smad2
Smad4
Smad3
Atrophy
NO
NOS
Smad7
p70s6K
eEF2K
GSK3β
4E-BP1
MNST
rpS6
eIF2Bε
eIF4E
eIF2B
eEF2
5'-TOP mRNA
eIF2Bε-Met-tRNA
Initiation
Elongation
Differentiation
of satellite cells
HSP's
HSP's
Folding
Translation
AAAAAAAAAA

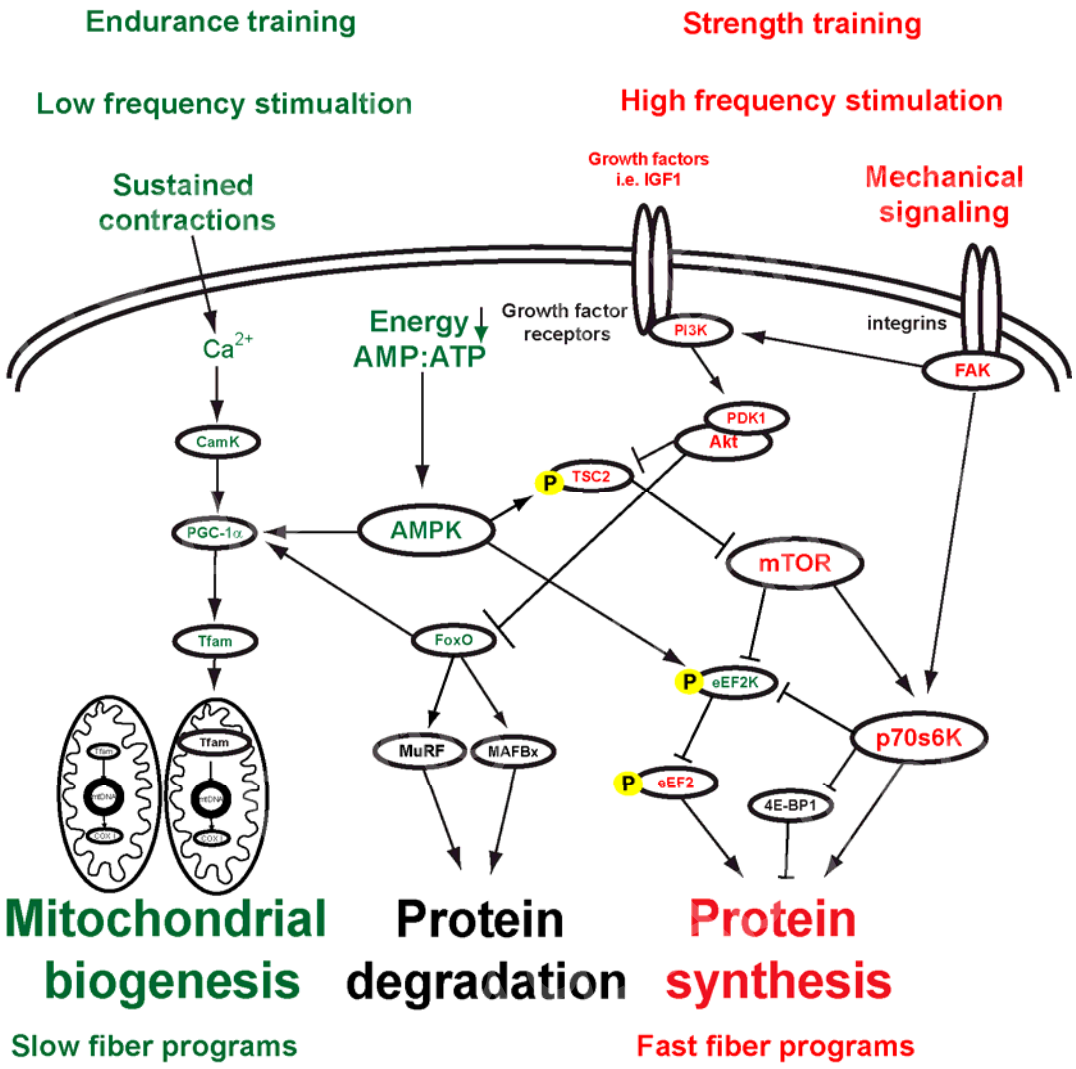


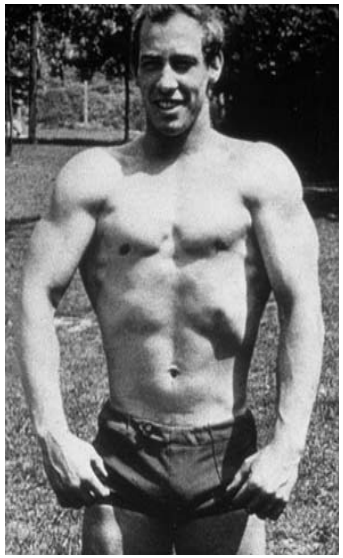
Strength training
quantitative changes - transcritionally driven
plus reqruitment of DNA from stem cells

Hoppeler et al. Comprehensive Physiology 2011

Endurance training – strength training interactions



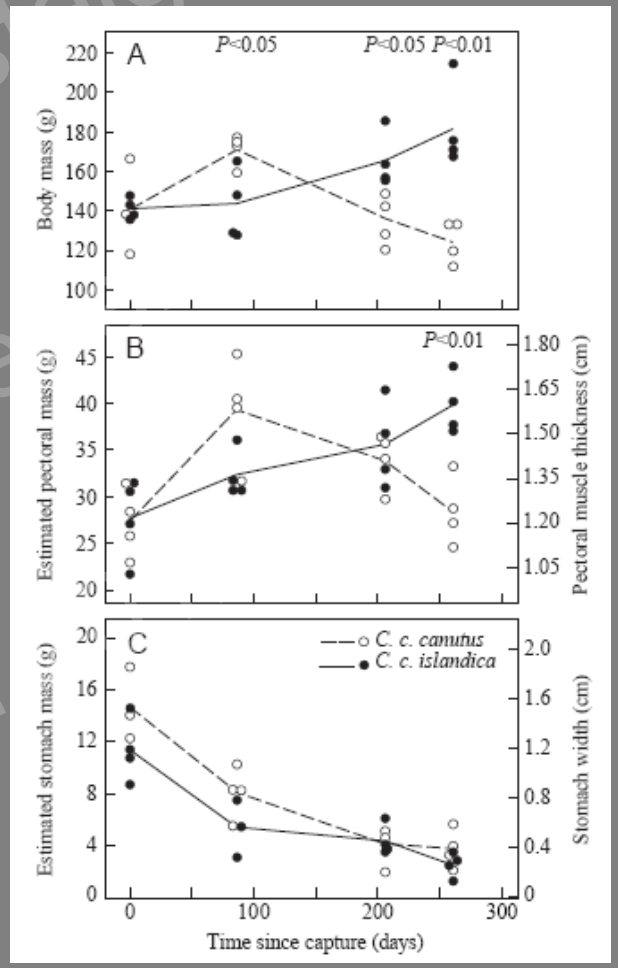


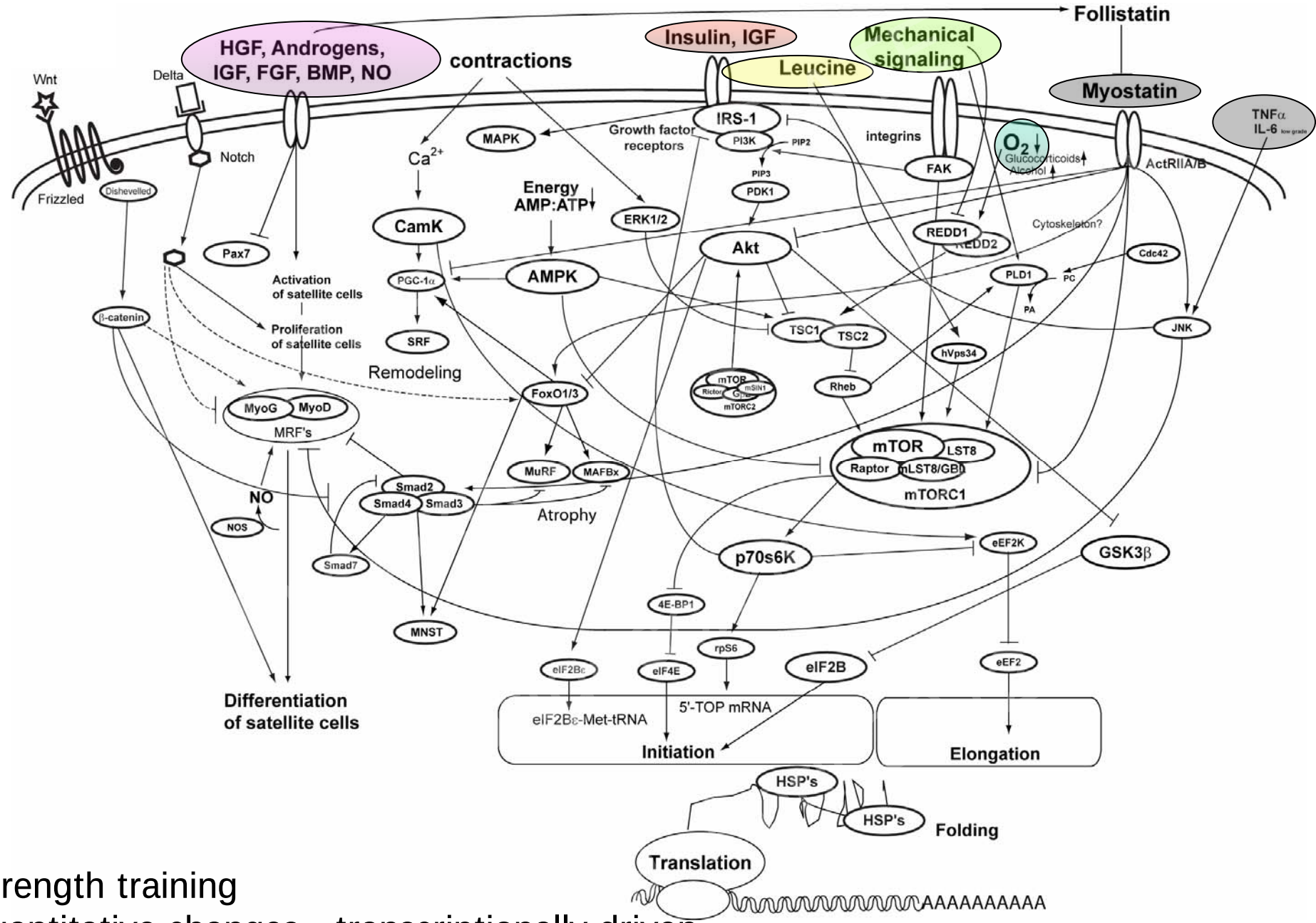


BODY-BUILDING WITHOUT POWER TRAINING: ENDOGENOUSLY REGULATED PECTORAL MUSCLE HYPERTROPHY IN CONFINED SHOREBIRDS (Canidris Canutus, red knot)

MAURINE W. DIETZ1,*, THEUNIS PIERSMA1,2 AND ANNE DEKINGA

The Journal of Experimental Biology 202, 2831–2837 (1999)





Strength training
quantitative changes - transcriptionally driven
plus reqruitment of DNA from stem cells

Hoppeler et al. Comprehensive Physiology 2011

Zusammenfassung

Die Anpassungsfähigkeit der Skelettmuskulatur basiert auf strukturellen Adaptationen

Dauerleistungstraining verändert Mitochondrien und Kapillaren, Krafttraining die Myofibrillen

Mechanische, hormonelle, neuronale und metabole Signale aktivieren multiple Signalkaskaden

Dauerleistungstraining wirkt hauptsächlich transkriptionell, Krafttraining vorallem translationell

Kraft- und Dauerleistungstraining interagieren auf molekularer Ebene

Species Spezifität liegt nicht in der Topologie sondern in den Knoteneigenschaften der regulatorischen Netzwerke begründet

Muscle Group Bern

Hans Hoppeler
Oliver Baum
Michael Vogt
Glen Lurman
Micah Gross
Franziska Graber
Liliane Gfeller
Ewald R Weibel

ORTHOPEDICS UPDATE

« Sportmedizin – für Einsteiger und Fortgeschrittene»

19. April 2012

ORTHOPEDICS UPDATE

« Sportmedizin – für Einsteiger und Fortgeschrittene»

19. April 2012

Summary

The malleability of skeletal muscle tissue is based on structural adaptations

Endurance training modifies mitochondria and capillaries, strength training the myofibrillar apparatus

Mechanical, hormonal, neuronal and metabolic signals activate multiple parallel signaling cascades

Endurance training is dominantly transcriptionally, strength training translationally modulated

Strength and endurance training interact on the molecular level

Species specificity is conveyed by node property not topology of signaling network

Descriptive features of endurance and strength training