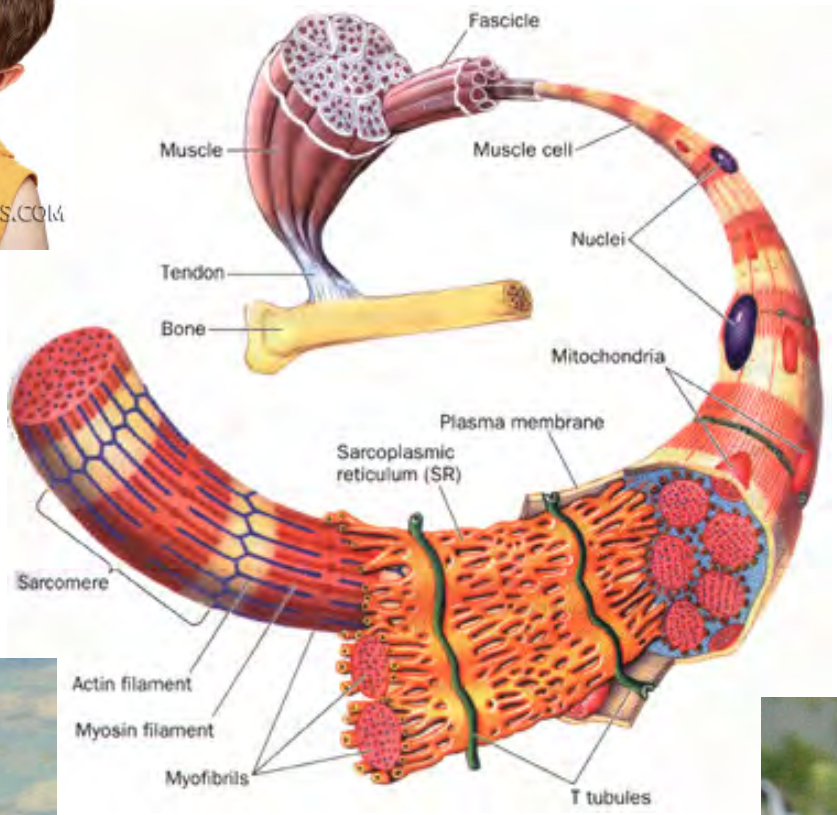
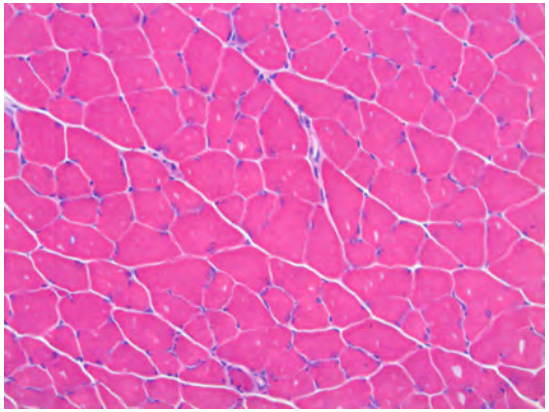
Signaling pathways that regulate skeletal muscle mass

Denis Guttridge, Ph.D.

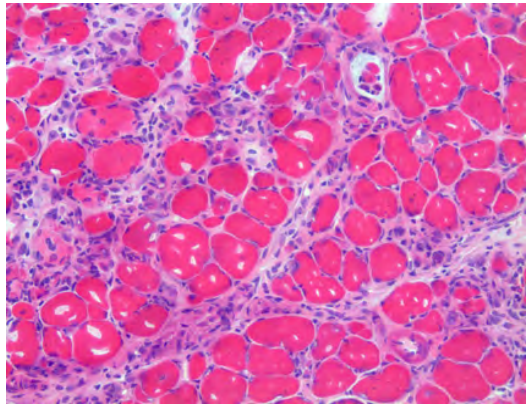
MVIMG 747, Neuromuscular Biology and Disease
May 24, 2012

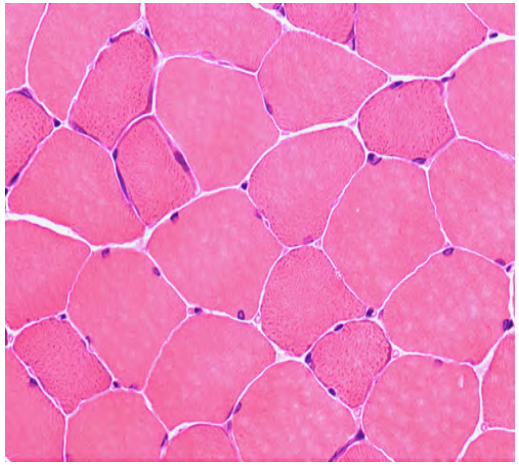

IPHOTOS.COM


Fascicle
Muscle
Muscle cell
Nuclei
Tendon
Bone
Mitochondria
Plasma membrane
Sarcoplasmic reticulum (SR)
Sarcomere
Actin filament
Myosin filament
Myofibrils
T tubules

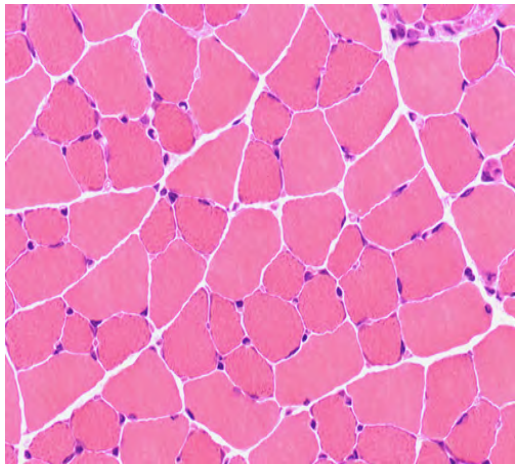


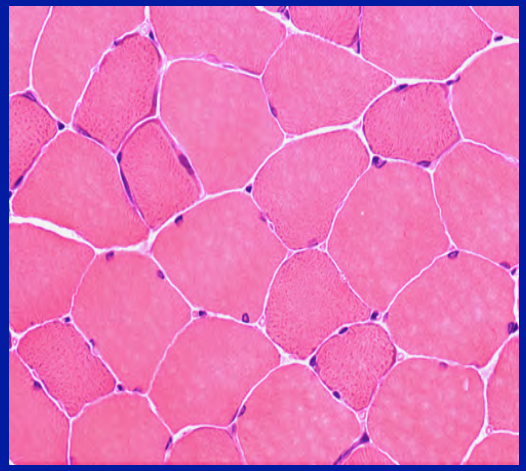
dystrophy

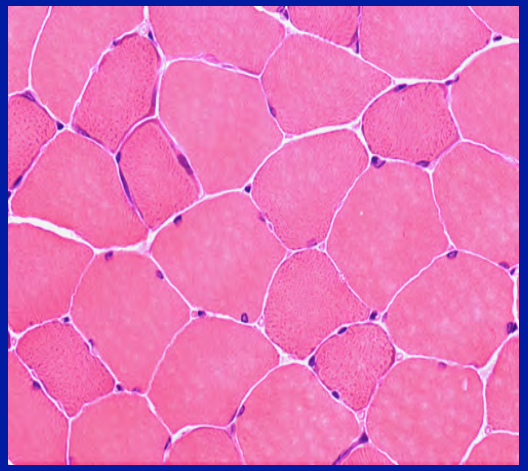




atrophy

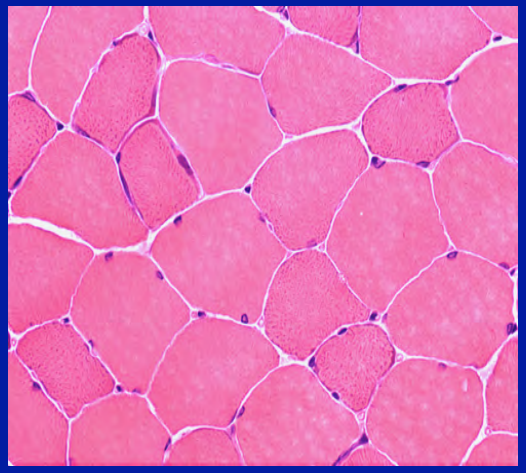


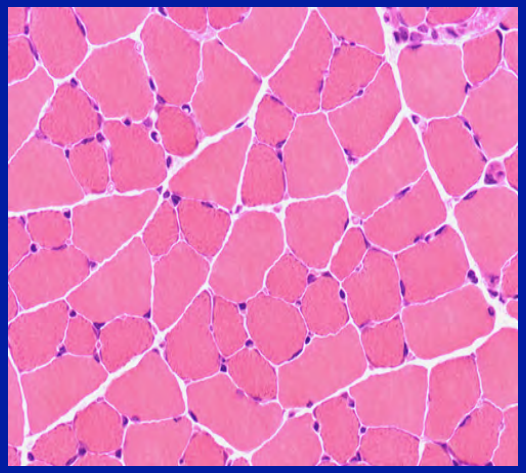


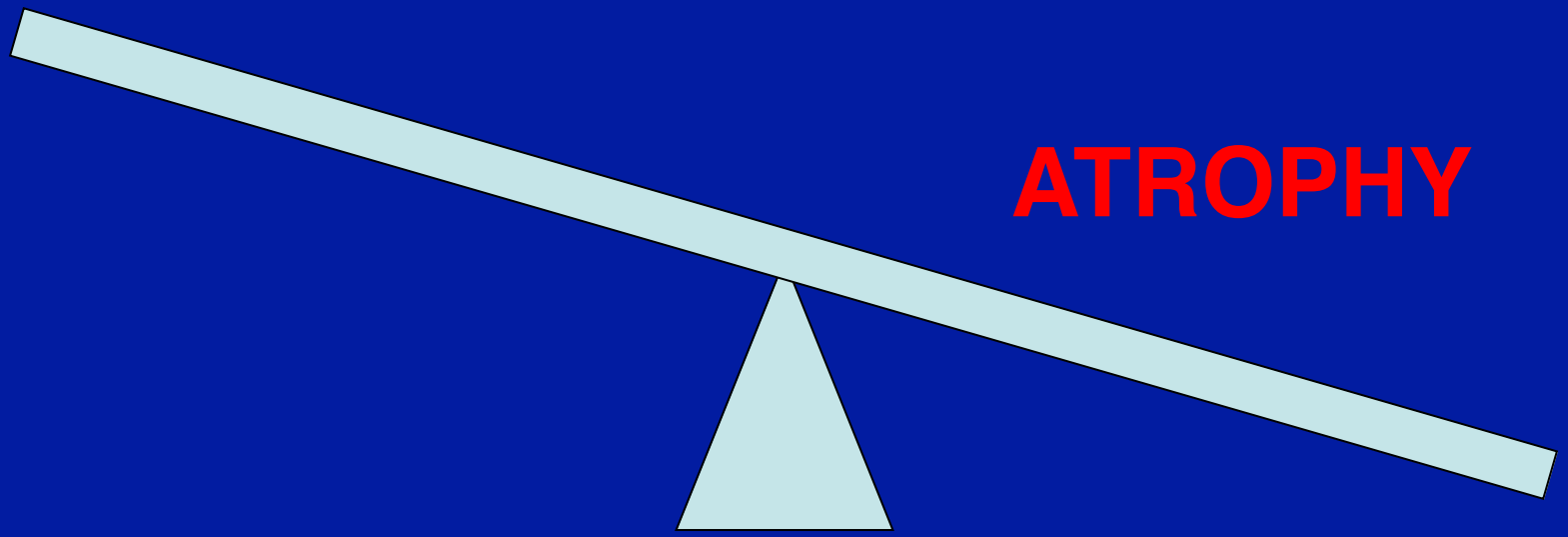


HYPERTROPHY

ATROPHY







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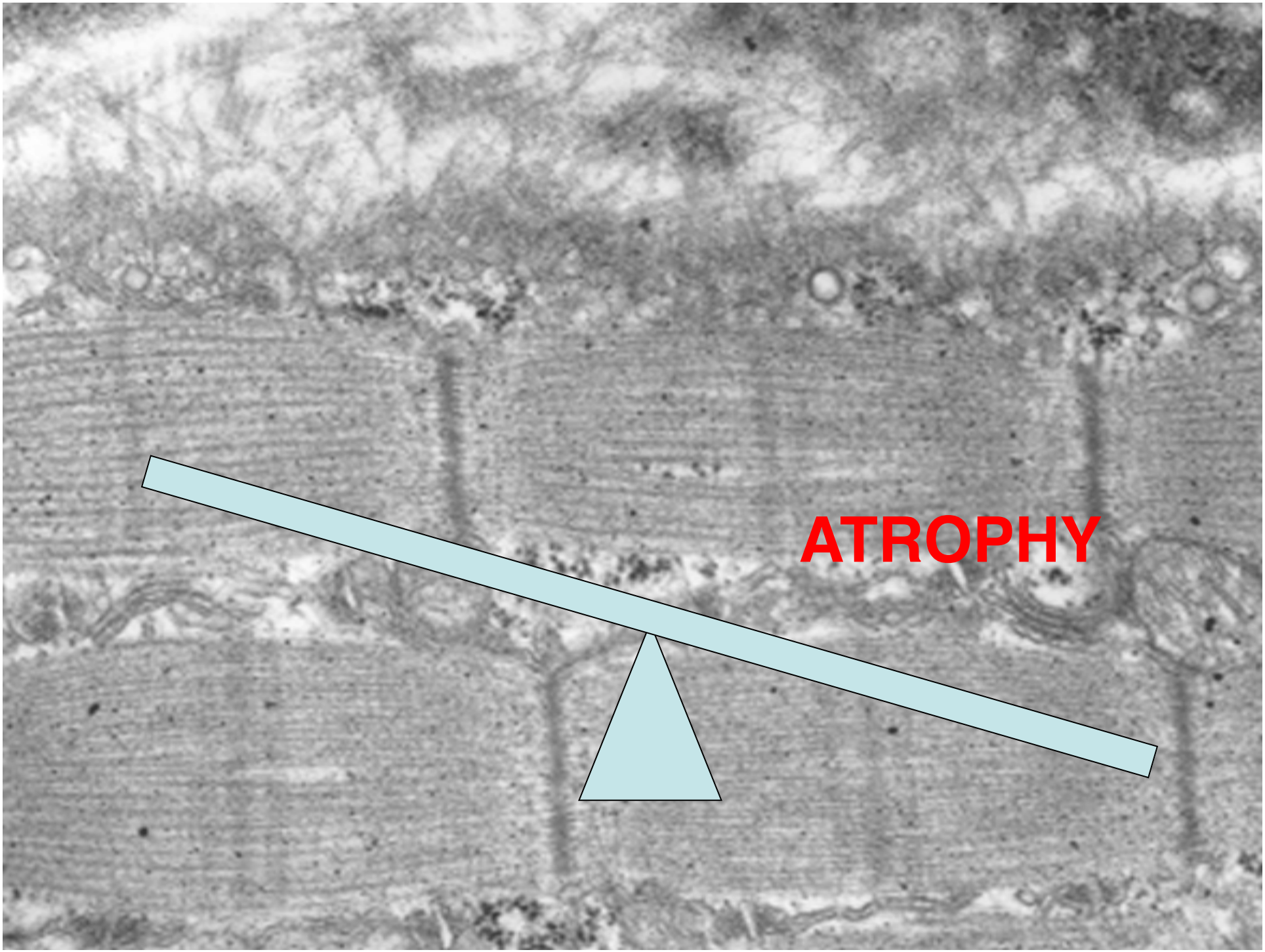
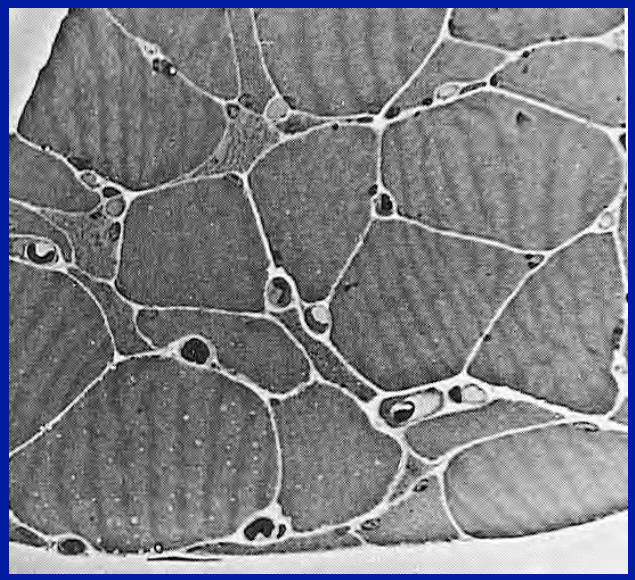
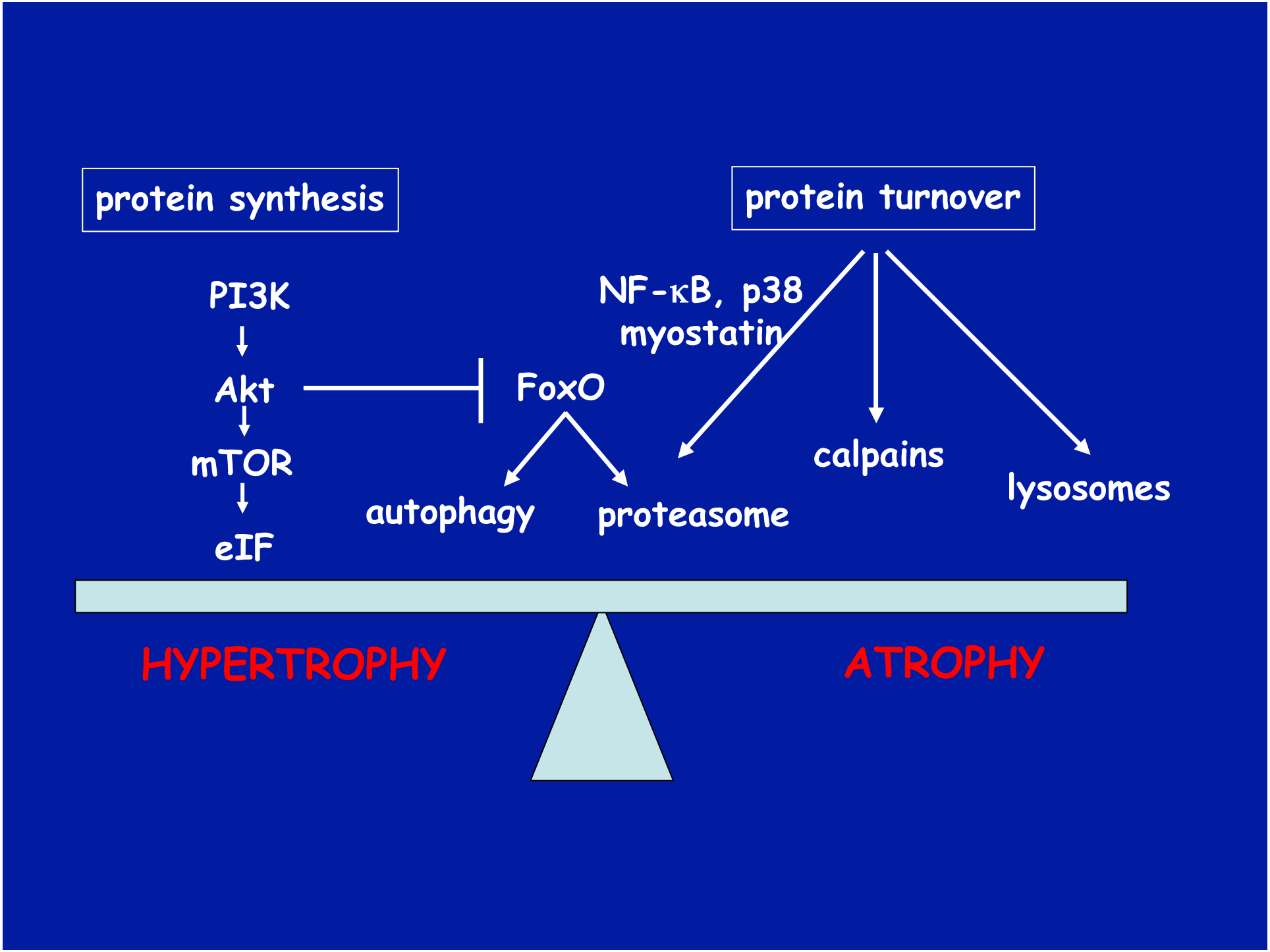

ATROPHY

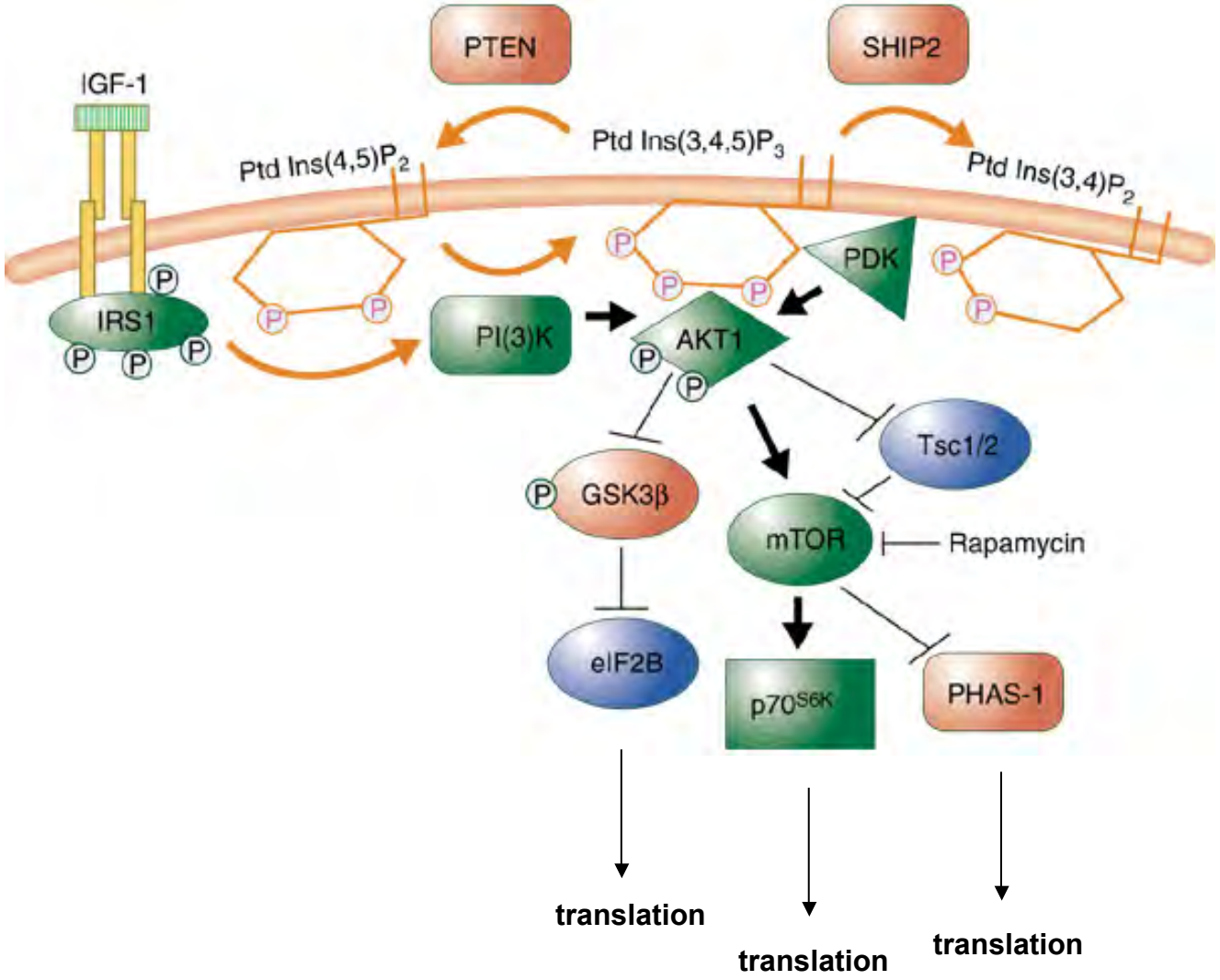
Cancer, COPD, Denervation, Renal Failure, (most forms of cachexia)



Human Biopsy (carcinoma)

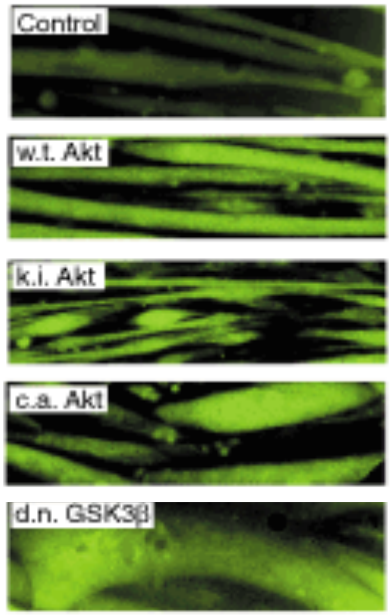
- **type II atrophy (fast twich fibers)**
- **increase vascularization (cancer)**
- **lack of immune infiltrates**
- **no strong indication of apoptosis**

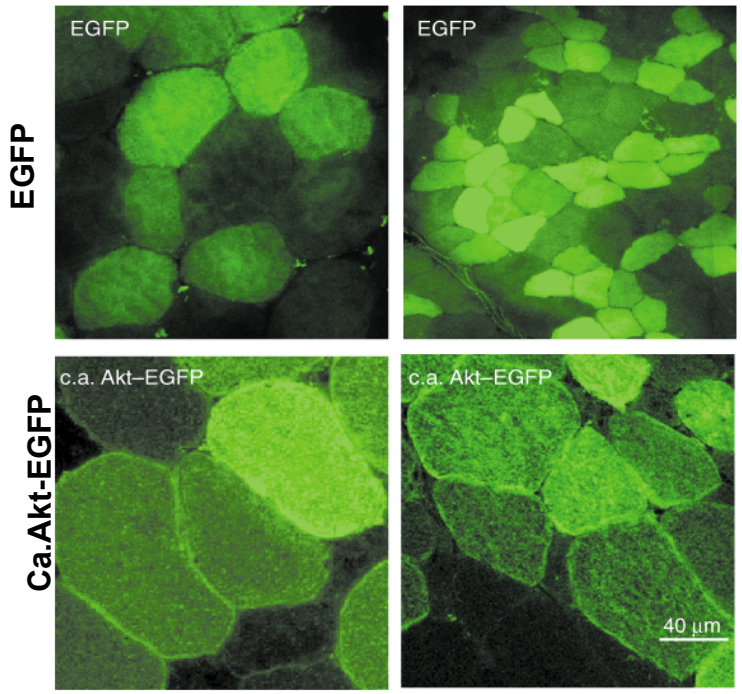

protein synthesis
protein turnover
PI3K
Akt
mTOR
eIF
FoxO
NF-κB, p38
myostatin
autophagy
proteasome
calpains
lysosomes
HYPERTROPHY
ATROPHY



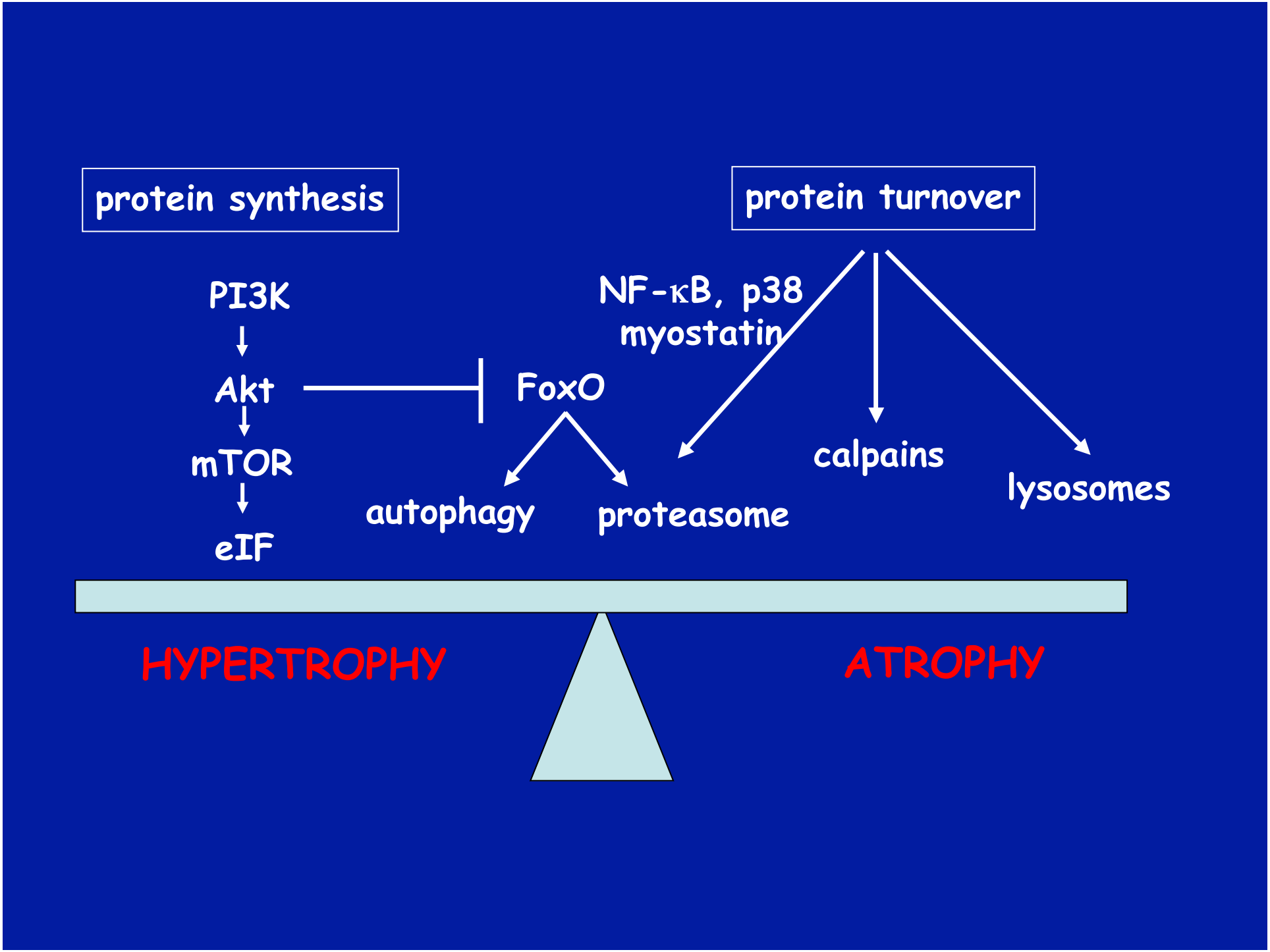
Glass, D.J., Nature Cell Biol., 2003

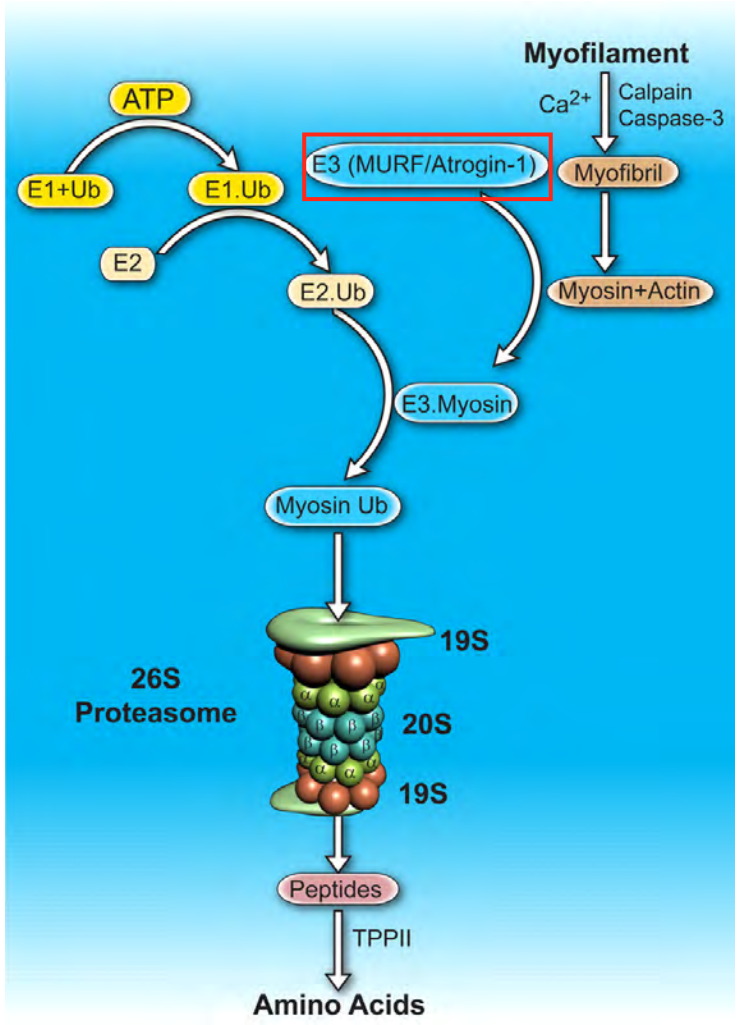
C2C12 myofibers



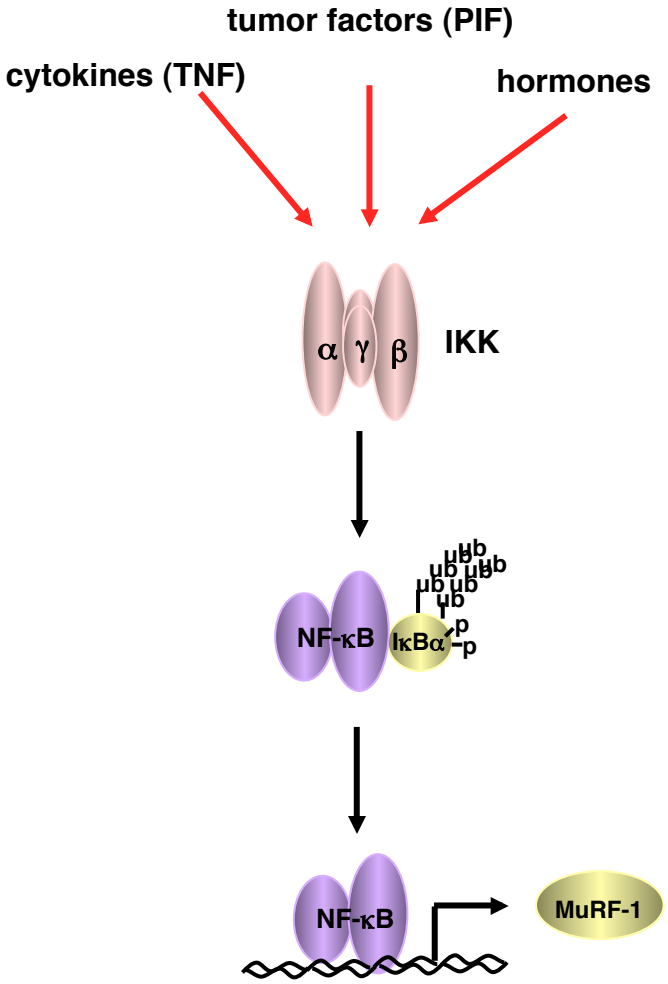


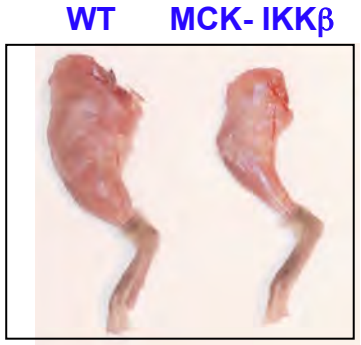
Bodine et al., Nature Cell Biol., 2001

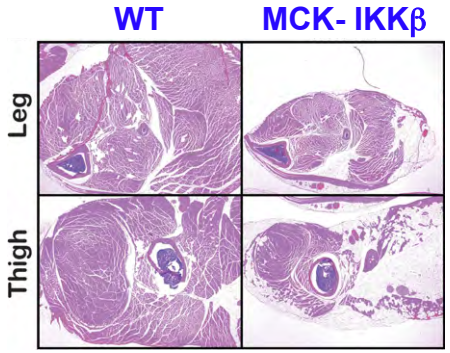

protein synthesis
protein turnover
PI3K
Akt
mTOR
eIF
FoxO
NF-κB, p38
myostatin
autophagy
proteasome
calpains
lysosomes
HYPERTROPHY
ATROPHY

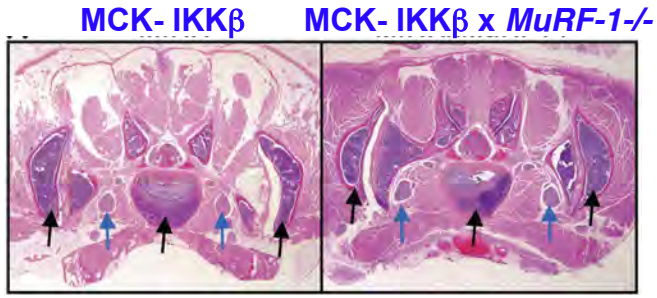


Tisdale, M. J. Physiol. Rev., 2009









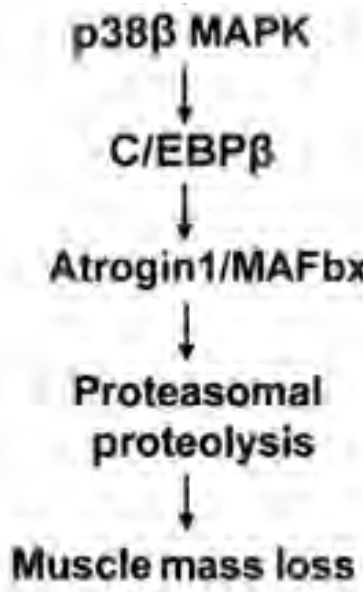
Cai et al., Cell, 2004

The EMBO Journal (2011) 30, 4323–4335 | © 2011 European Molecular Biology Organization | All Rights Reserved 0261-4189/11
www.embojournal.org

THE EMBO JOURNAL

C/EBPβ mediates tumour-induced ubiquitin ligase atrogin1/MAFbx upregulation and muscle wasting

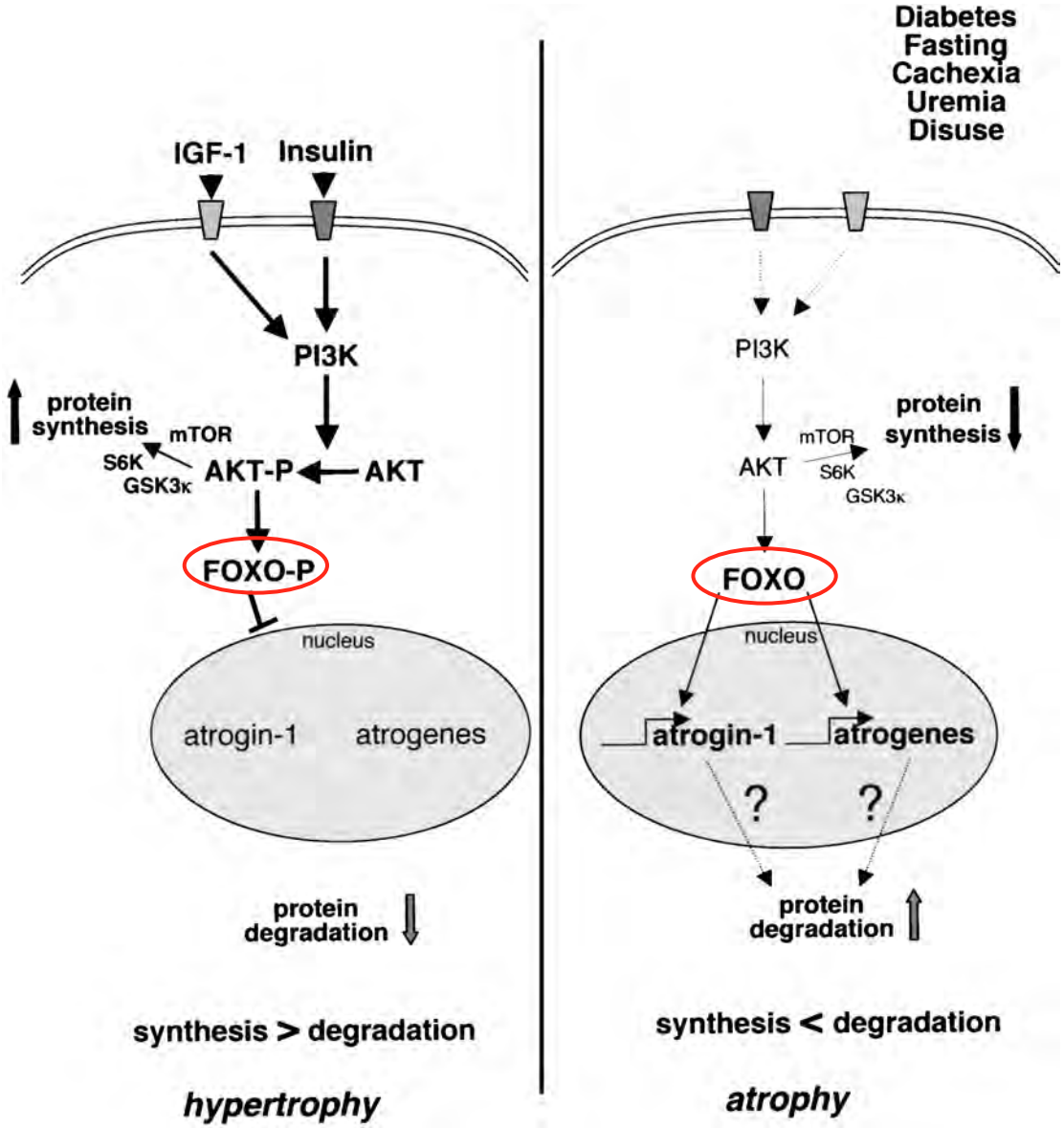
Guohua Zhang[1], Bingwen Jin[2] and Yi-Ping Li[1,*]



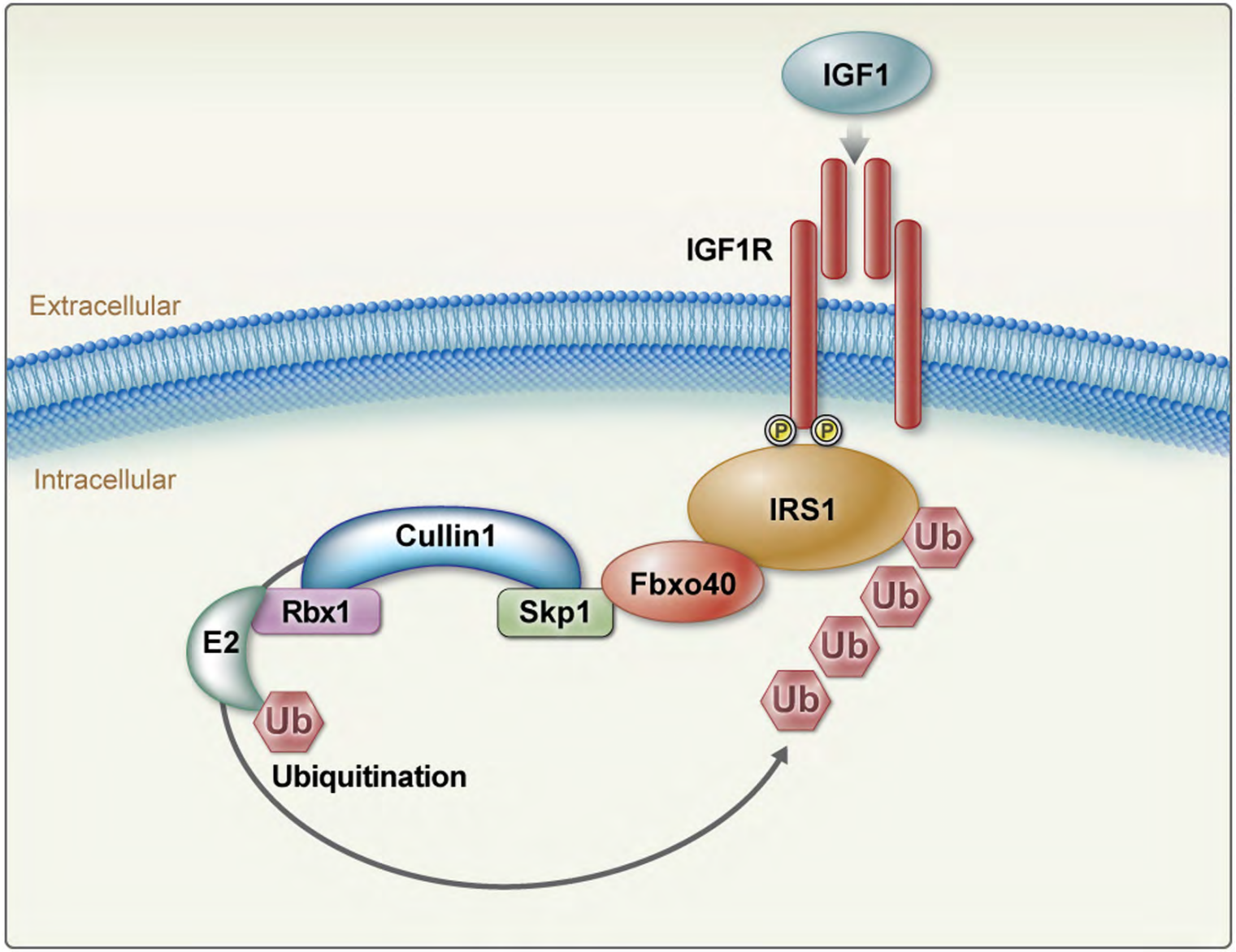
Specific to the β isoform of p38

(Not MuRF-1)

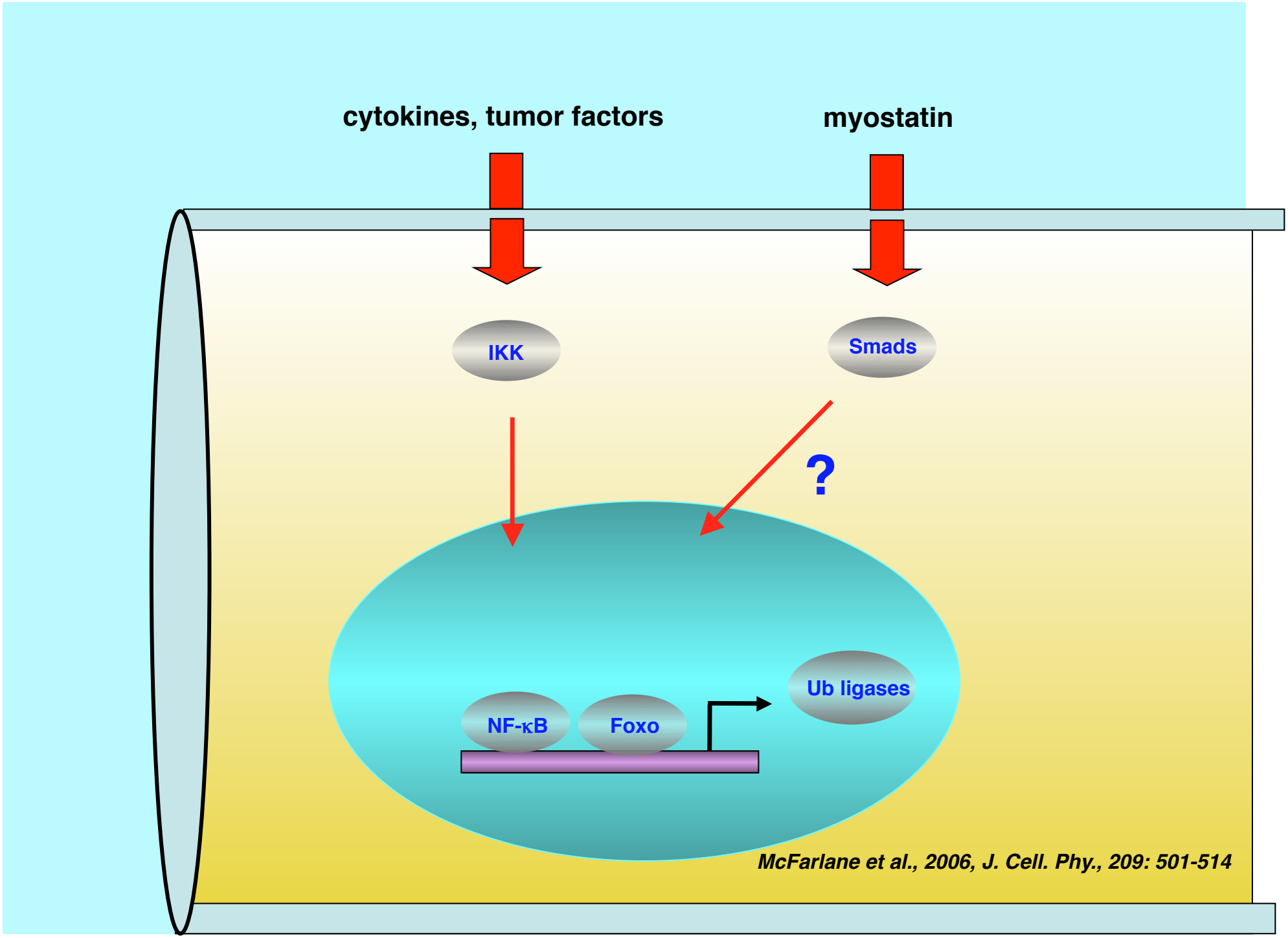
(MyHC protein and RNA are both reduced by 80%

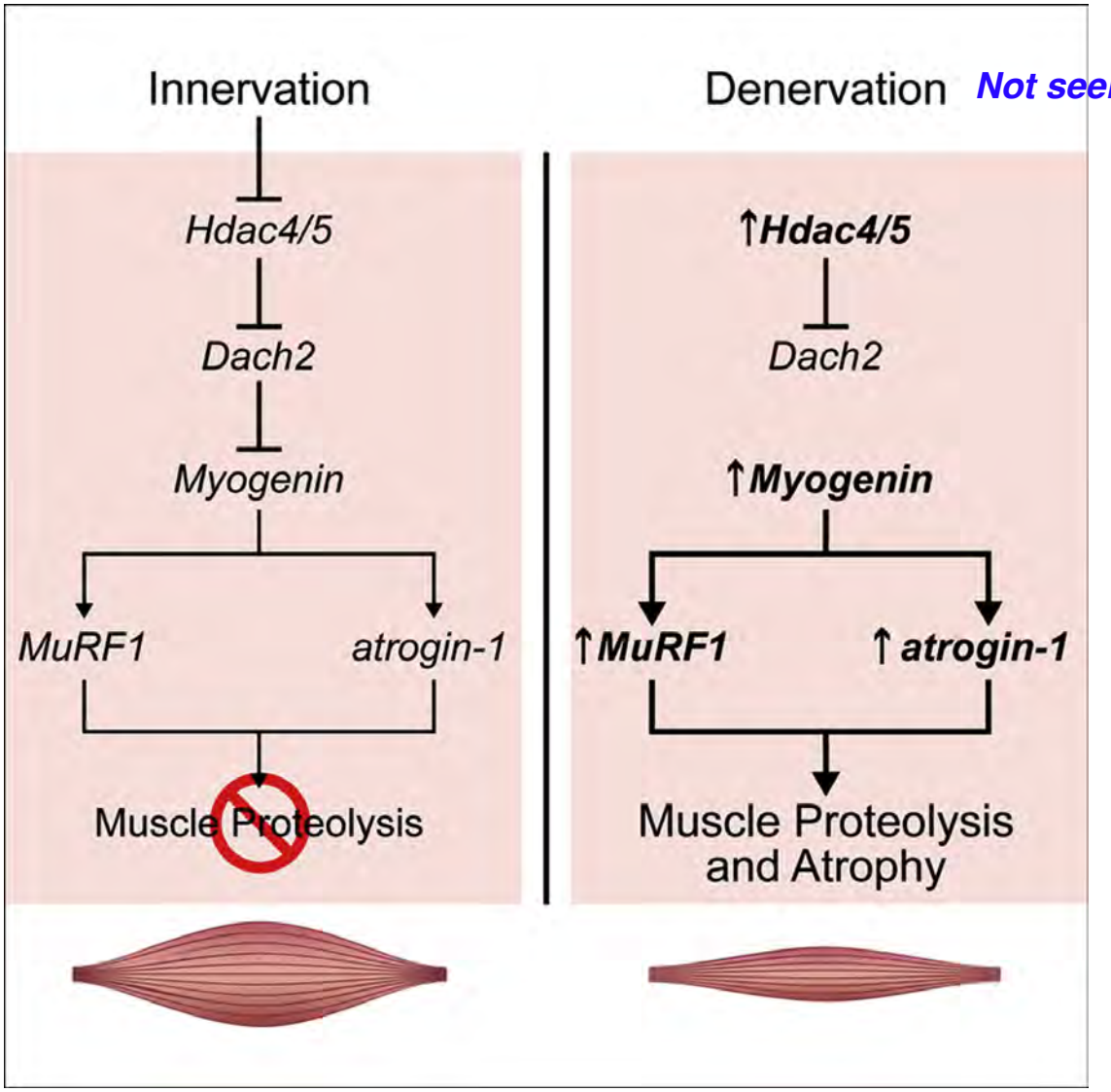


Sandri et al., Cell, 2004

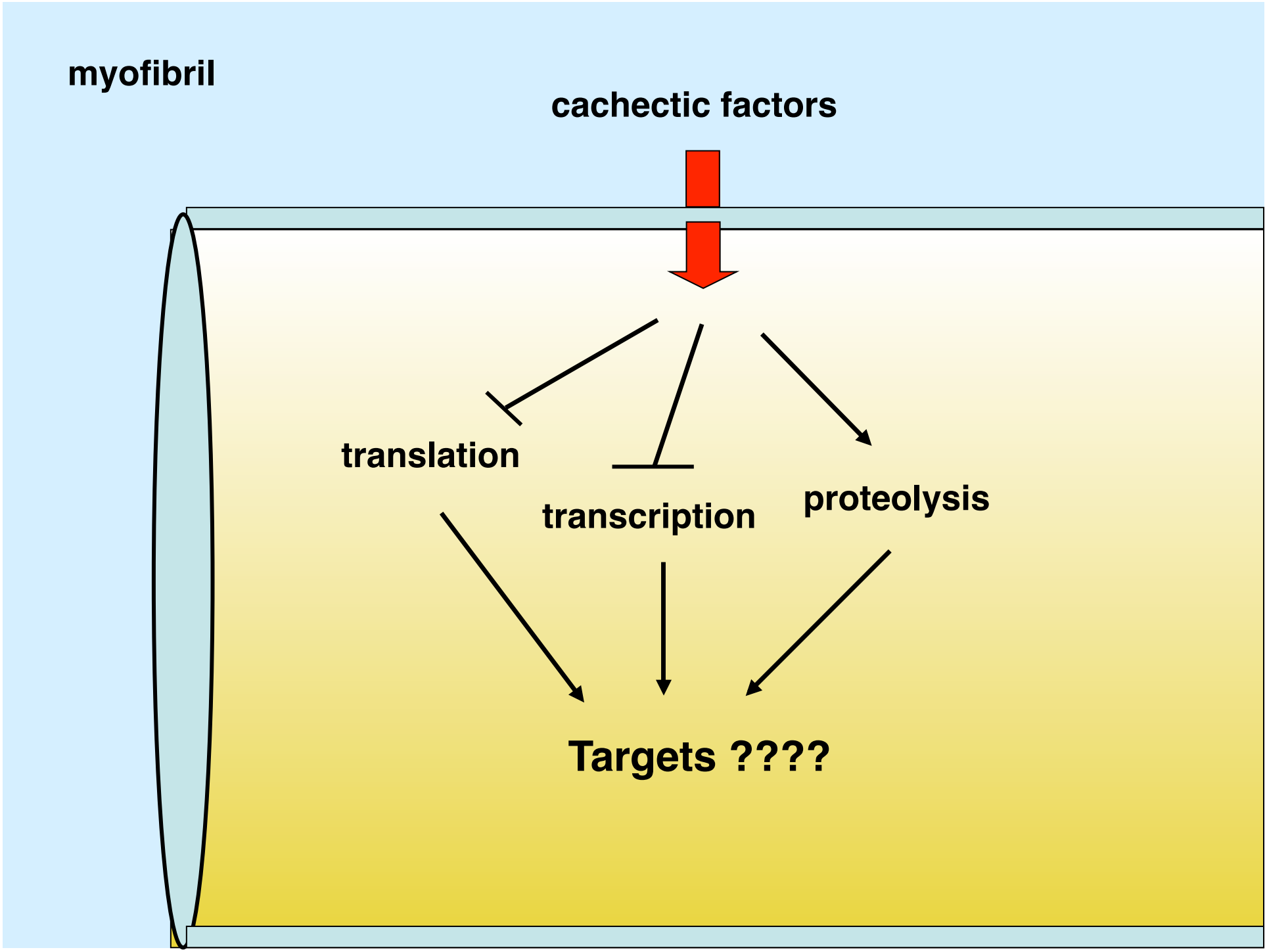


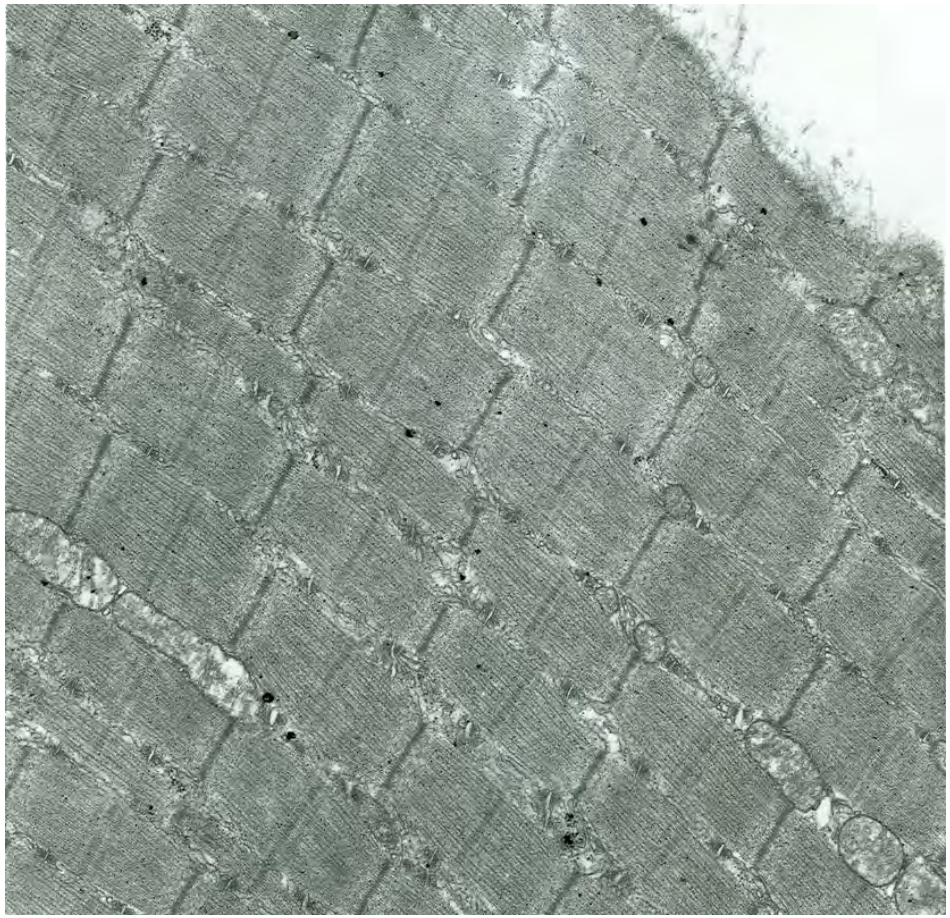
Shi et al., Dev Cell, 2011, 5: 835

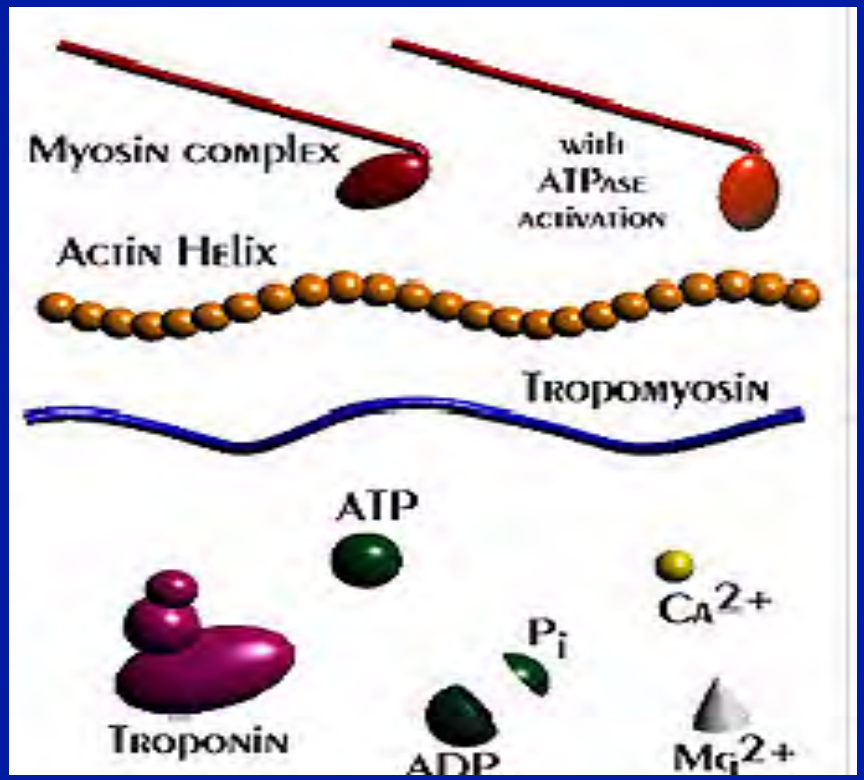

cytokines, tumor factors
myostatin
IKK
Smads
?
NF-κB
Foxo
Ub ligases
McFarlane et al., 2006, J. Cell. Phy., 209: 501-514

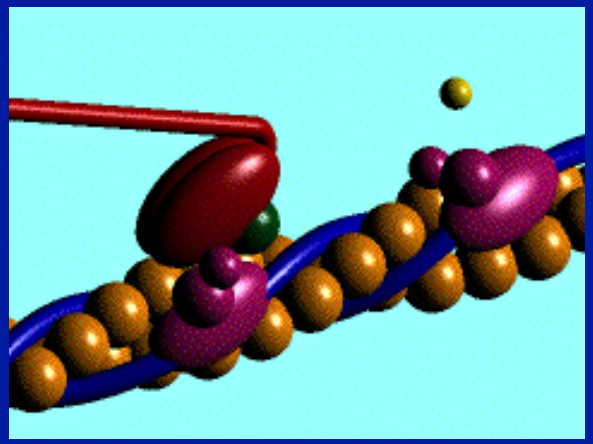


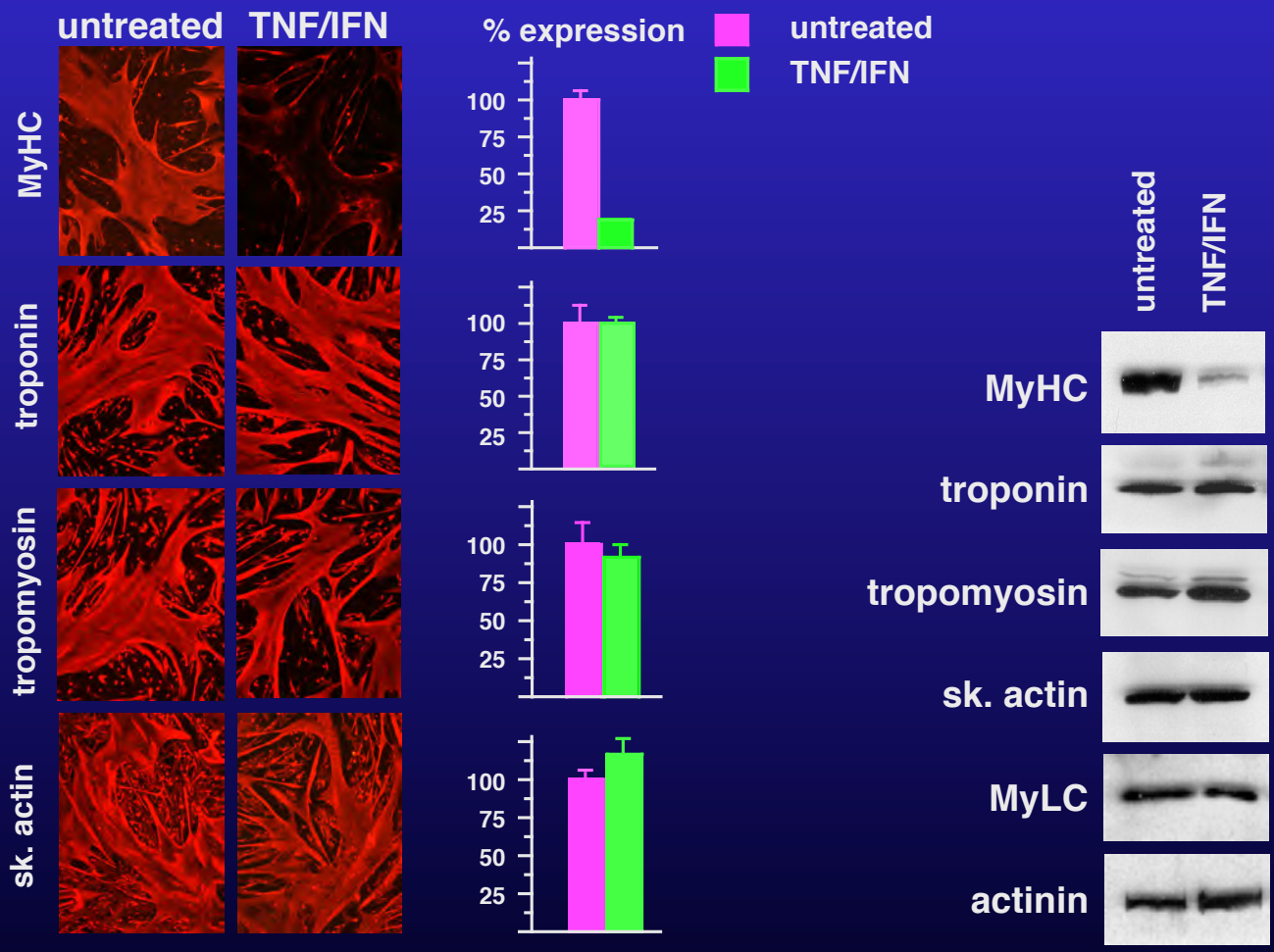
Moresi et al., Cell, 2010, 143: 35

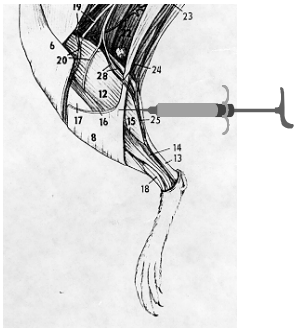

myofibril
cachectic factors
translation
transcription
proteolysis
Targets ????

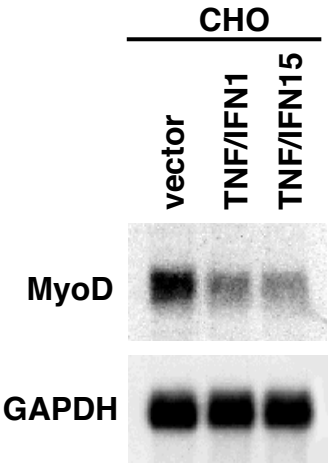


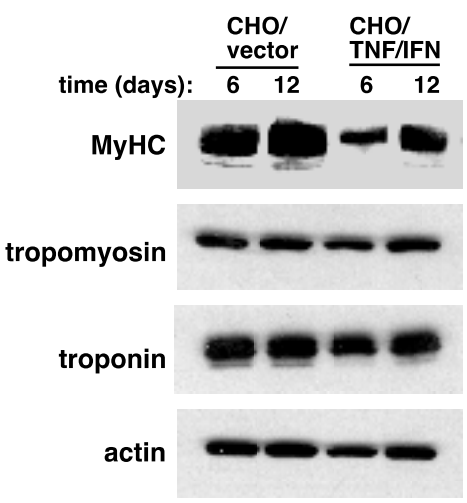

Myosin complex
with
ATPase
activation
Actin Helix
Tropomyosin
ATP
Troponin
Pi
ADP
Ca2+
Mg2+



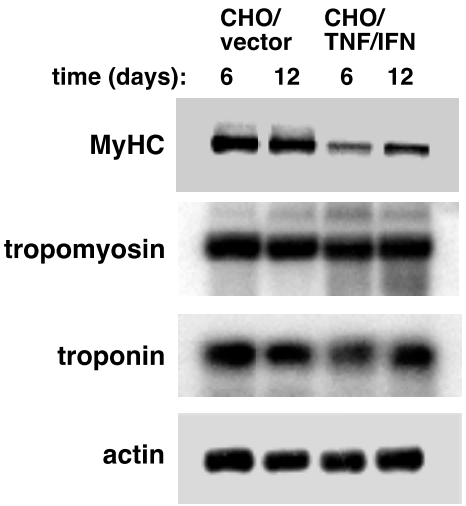

untreated
TNF/IFN
MyHC
troponin
tropomyosin
sk. actin
% expression
untreated
TNF/IFN
100
75
50
25
100
75
50
25
100
75
50
25
100
75
50
25
untreated
TNF/IFN
MyHC
troponin
tropomyosin
sk. actin
MyLC
actinin





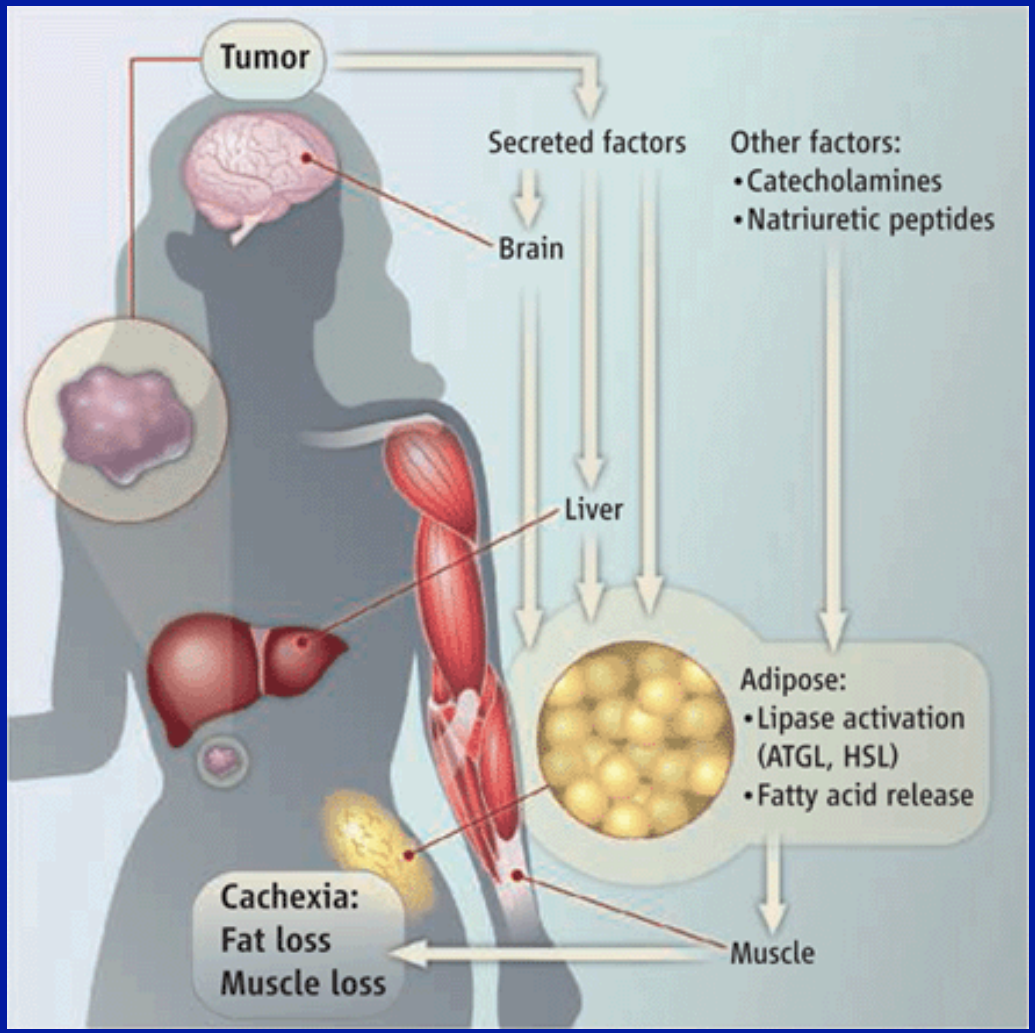


Westerns

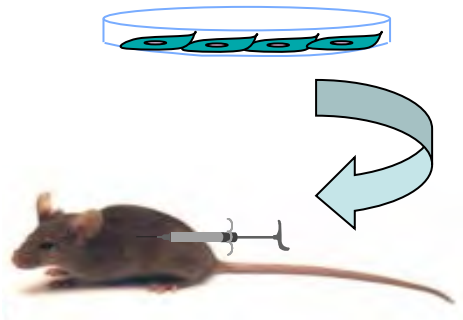


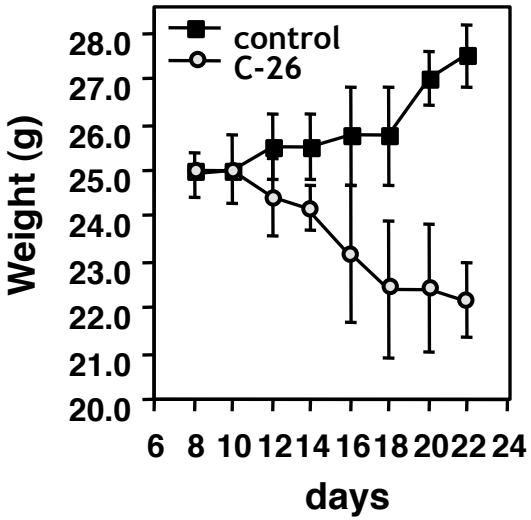
Northerns

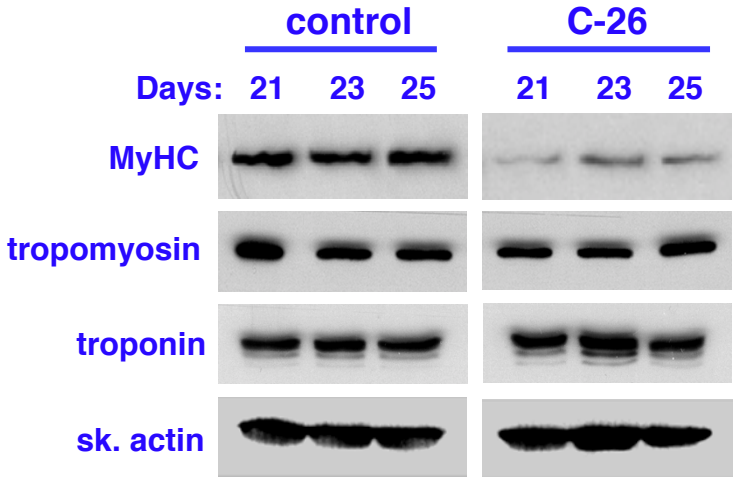
Cancer Cachexia



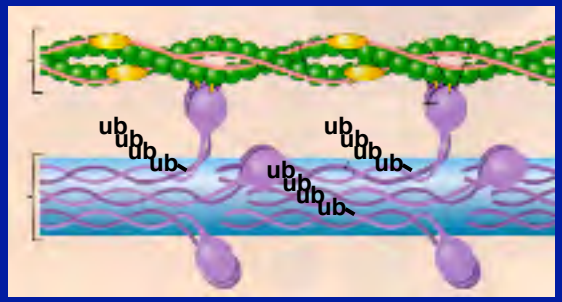
Colon-26 (C-26) Adenocarcinoma Cachexia Model







Acharyya et al., JCI, 2004


ub
ub
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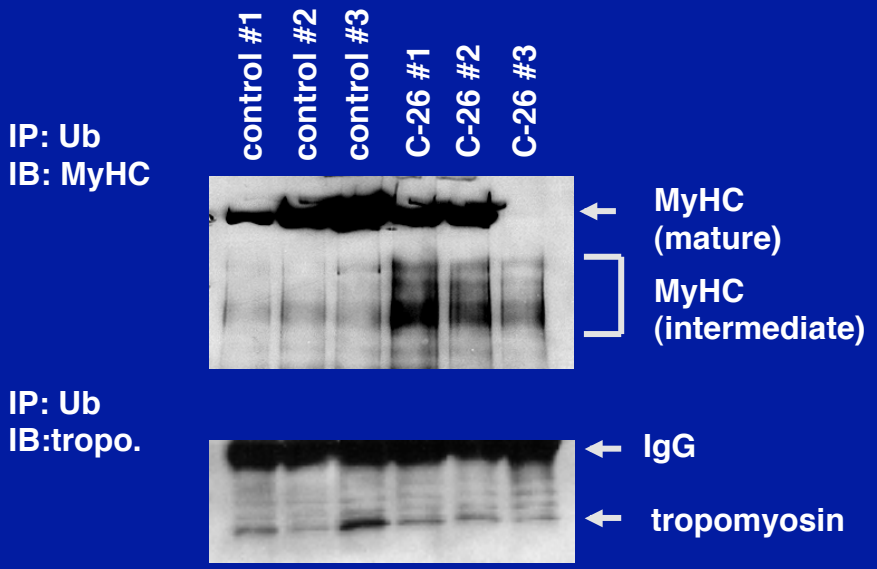
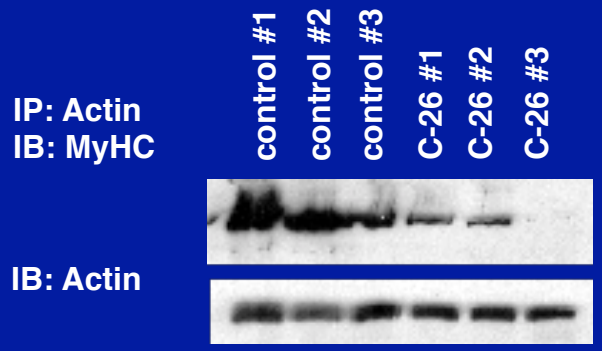
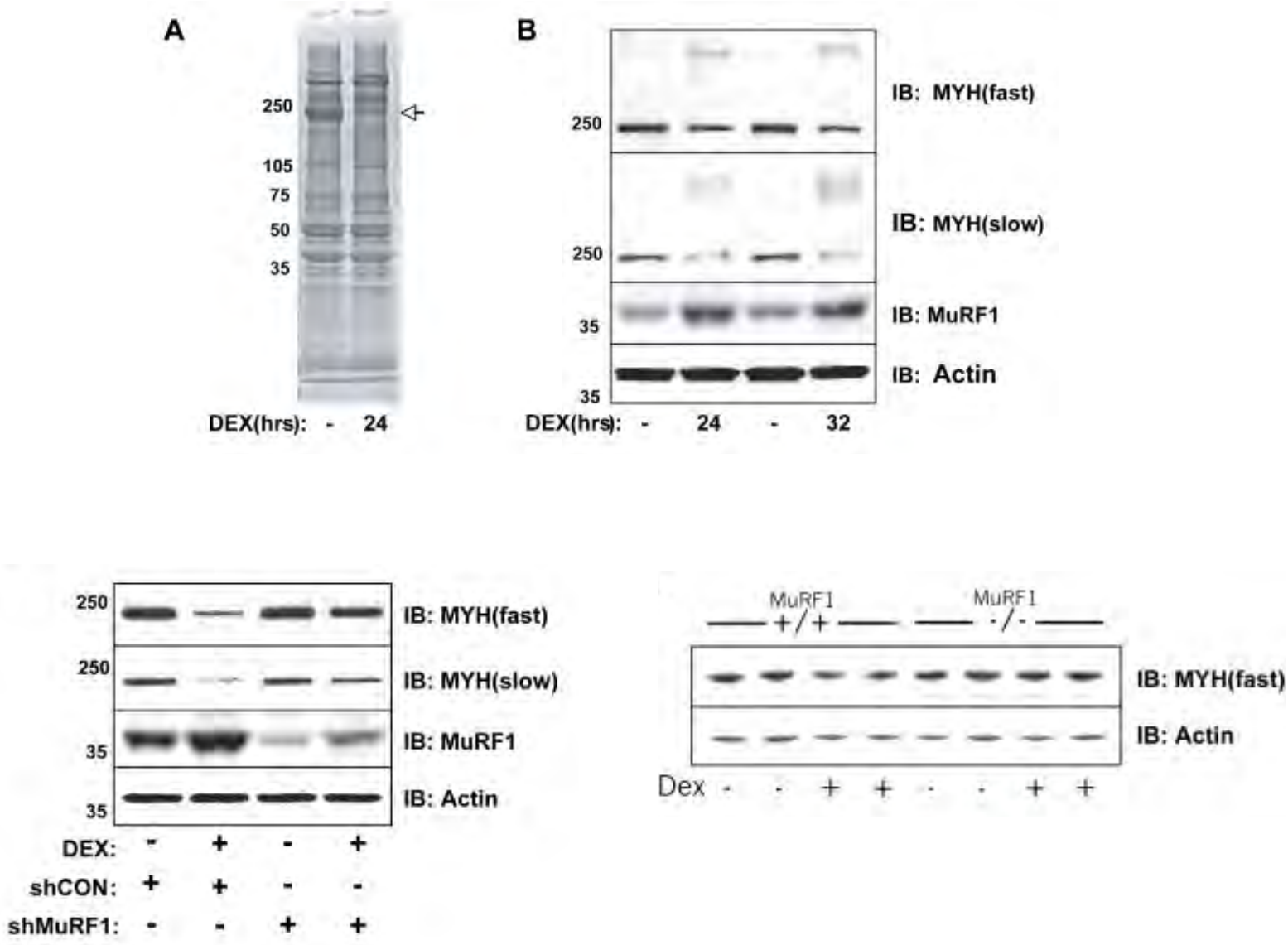
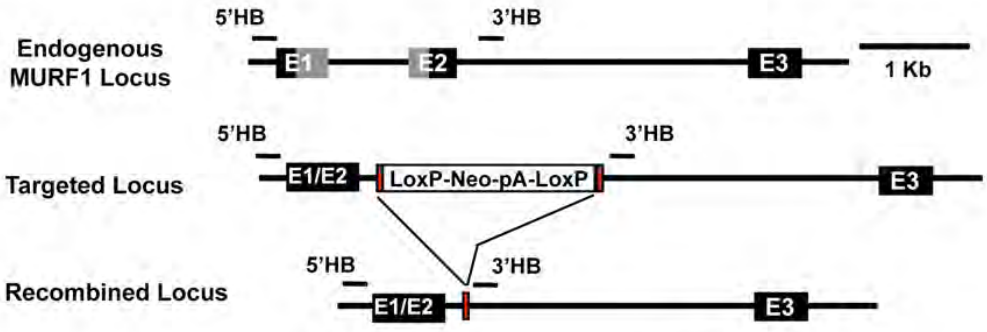

IP: Ub
IB: MyHC
control #1
control #2
control #3
C-26 #1
C-26 #2
C-26 #3
MyHC
(mature)
MyHC
(intermediate)
IP: Ub
IB:tropo.
IgG
tropomyosin

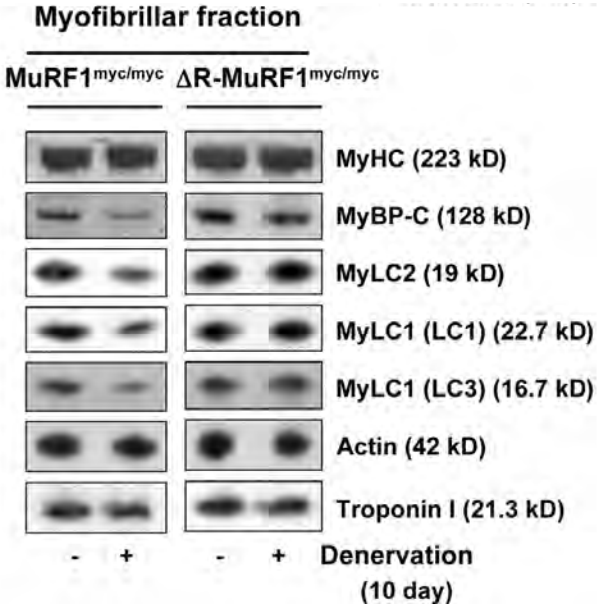

IP: Actin
IB: MyHC
control #1
control #2
control #3
C-26 #1
C-26 #2
C-26 #3
IB: Actin



Clarke et al., Cell Metabolism, 2007

△R-MuRF-1





Cohen et al., J. Cell Biol, 2009

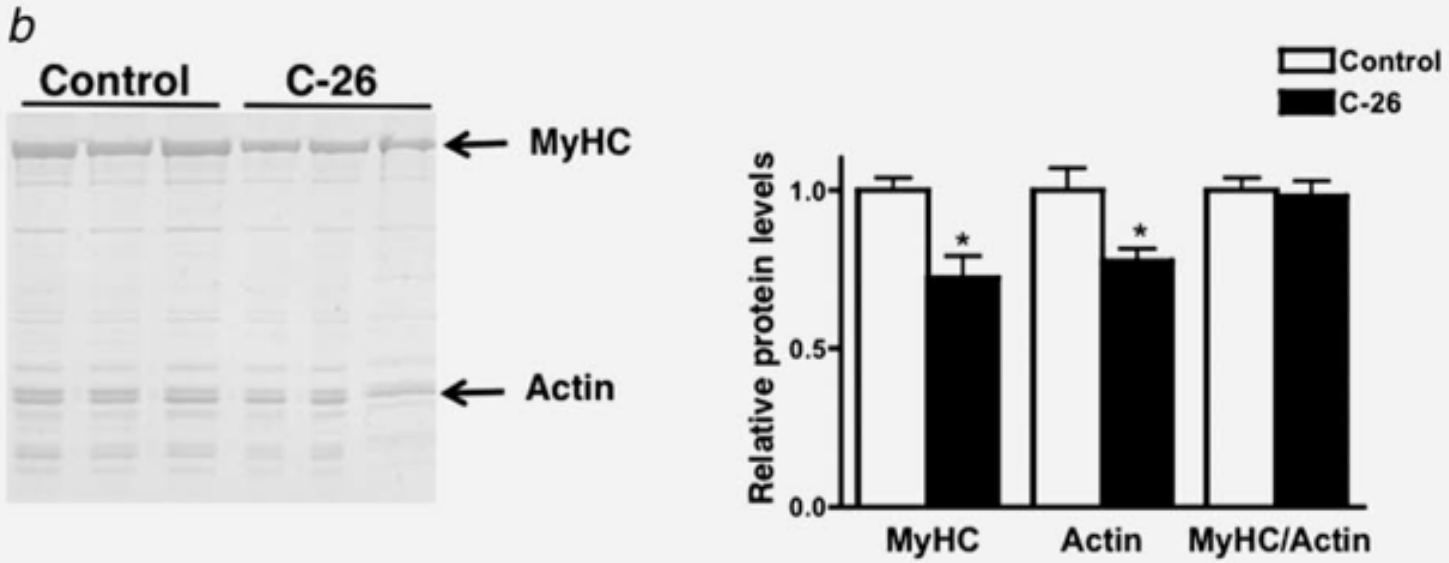
uicc
global cancer control

IJC
International Journal of Cancer

Myosin heavy chain is not selectively decreased in murine cancer cachexia

Pippa F. Cosper and Leslie A. Leinwand

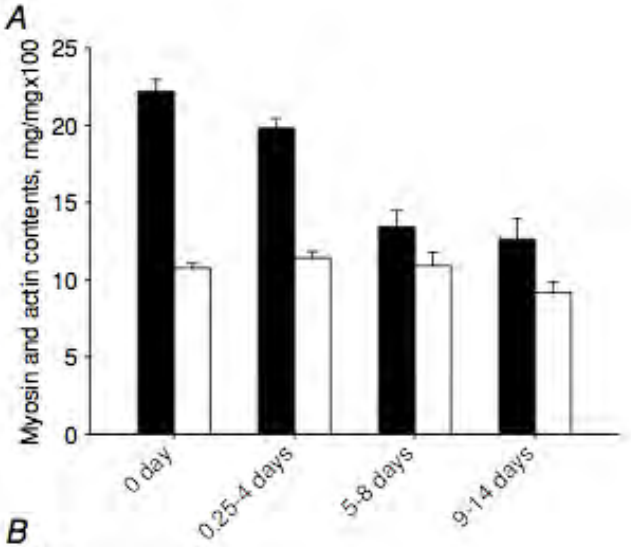
Department of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder, Boulder, CO

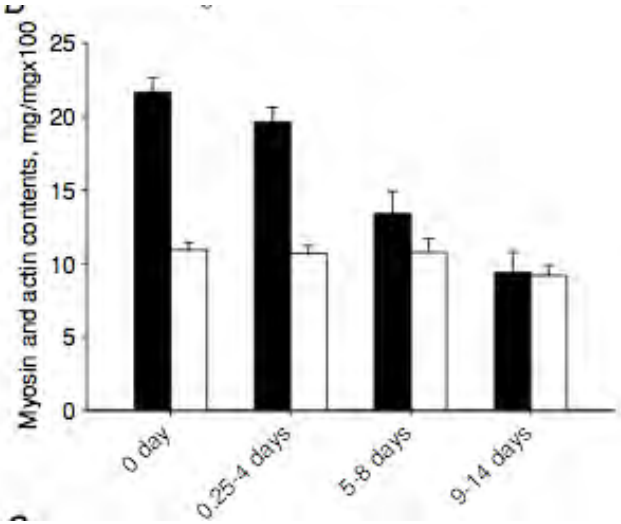


J Physiol 589.8 (2011) pp 2007–2026

Preferential skeletal muscle myosin loss in response to mechanical silencing in a novel rat intensive care unit model: underlying mechanisms

Julien Ochala[1], Ann-Marie Gustafson[1], Monica Llano Diez[1], Guillaume Renaud[1], Meishan Li[1], Sudhakar Aare[1], Rizwan Qaisar[1], Varuna C. Banduseela[1], Yvette Hedström[1], Xiaorui Tang[2], Barry Dworkin[1,2], G. Charles Ford[3], K. Sreekumaran Nair[3], Sue Perera[4], Mathias Gautel[4] and Lars Larsson[1,5]





Muscle Paralysis and Myosin Loss in a Patient with Cancer Cachexia

V. Banduseela[1,*], J. Ochala[1,*], K. Lamberg[2], H. Kalimo[3,4], L. Larsson[1,5]

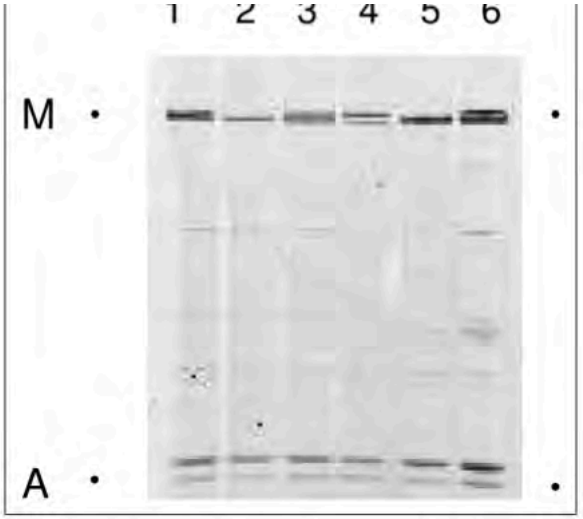
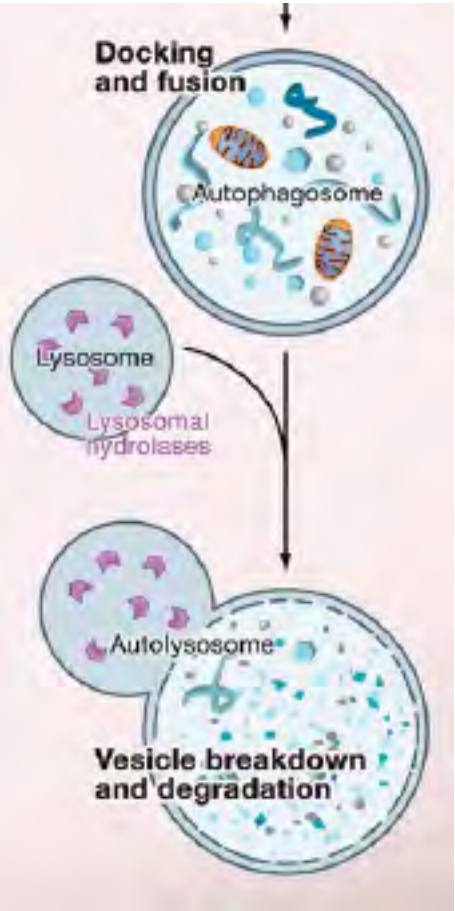
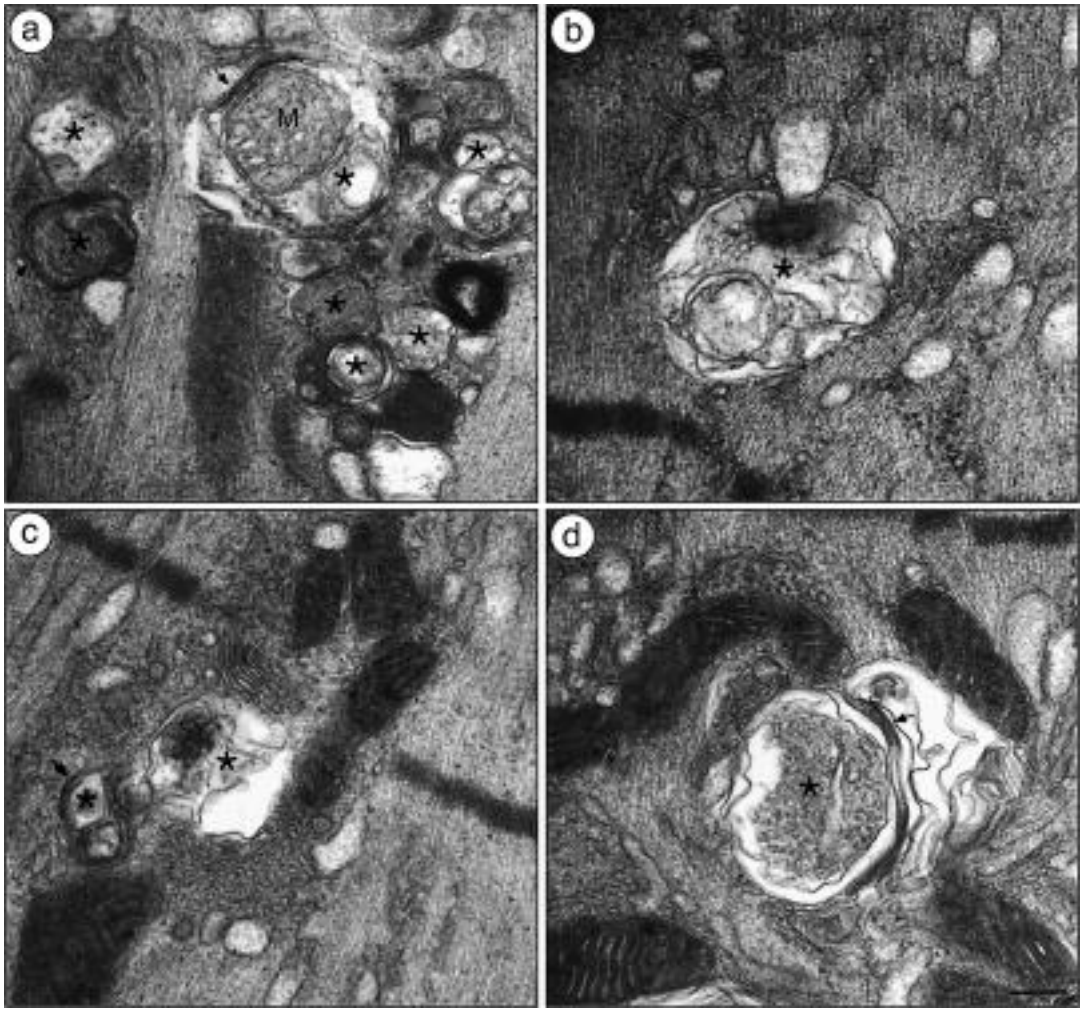


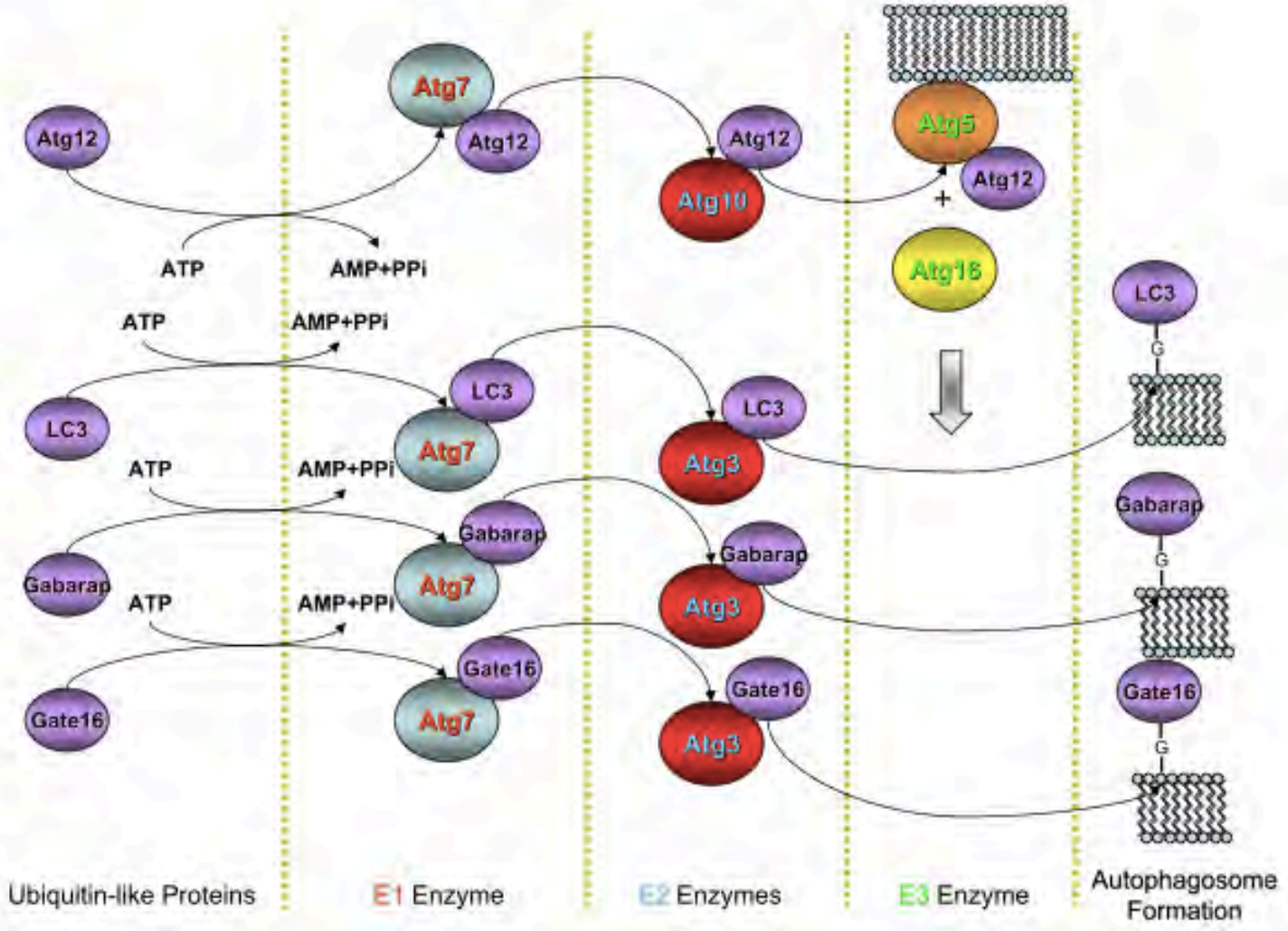
Figure 4. Myofibrillar protein separations on 12% SDS-PAGE in the patient with cancer cachexia (2, myosin:actin ratio 0.8), a patient with cachexia due to malnutrition (3, myosin:actin ratio 1.8), two healthy control subjects (1, myosin:actin ratio 2.0; 4, myosin:actin ratio 1.8), a patient with Charcot Marie-Tooths disease type 1 (5, myosin:actin ratio 2.1) and type type 2 (6, myosin:actin ratio 2.1). The part of the gel with the myosin (M) and actin (A) bands are shown.



Levine & Kroemer, 2008, Cell, 132: 27



Wang et al., G&D, 2005, 19:1715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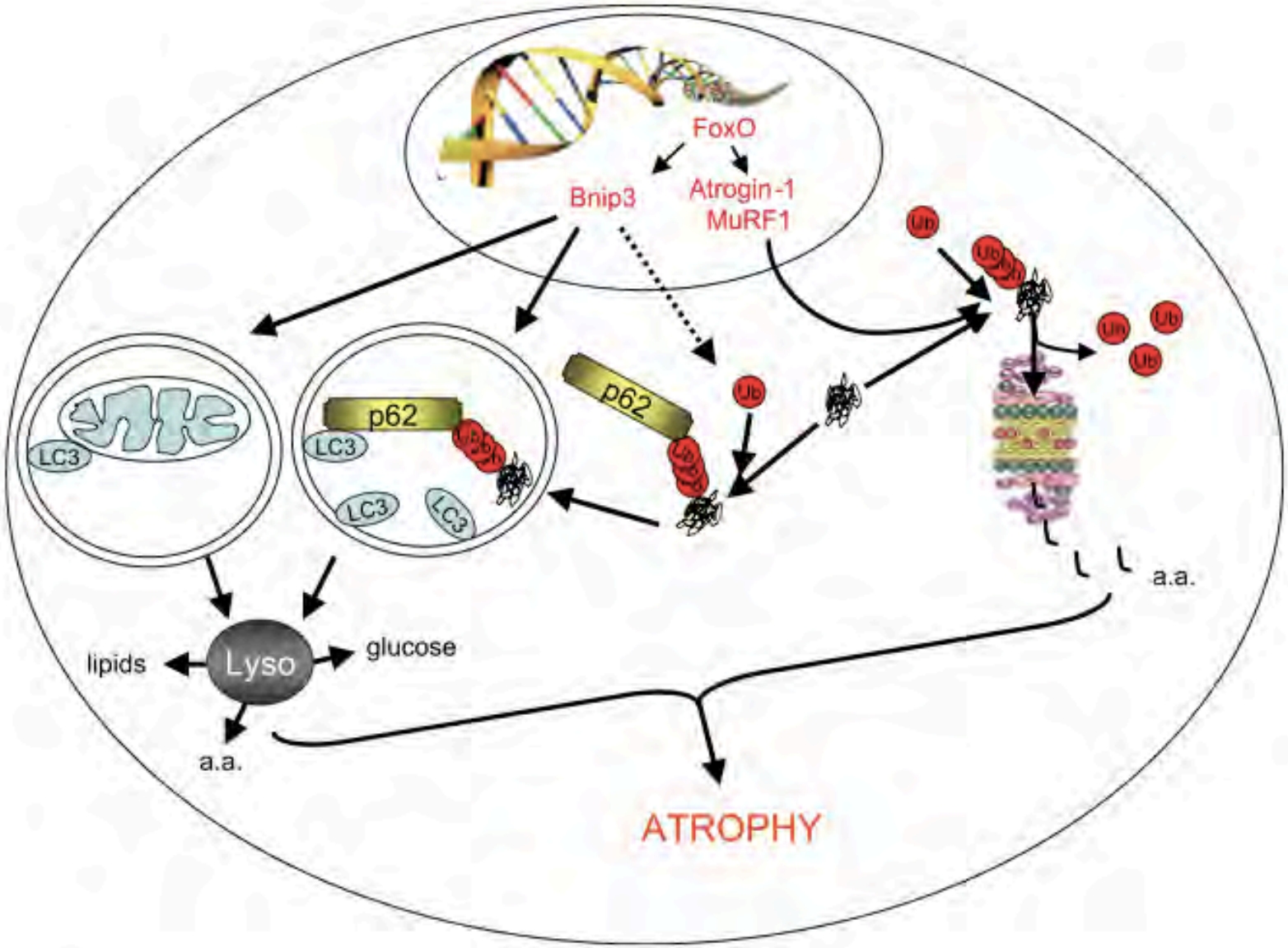
Atg7
Atg12
ATP
AMP+PPi
Atg12
Atg10
Atg5
Atg12
+
Atg16
LC3
G
ATP
AMP+PPi
LC3
LC3
Atg7
Atg3
ATP
AMP+PPi
Gabarap
Gabarap
Atg7
Gabarap
Atg3
ATP
AMP+PPi
Gate16
Gate16
Atg7
Gate16
Atg3
Ubiquitin-like Proteins
E1 Enzyme
E2 Enzymes
E3 Enzyme
Autophagosome Formation


FoxO
Bnip3
Atrogin-1
MuRF1
Ub
LC3
p62
LC3
LC3
LC3
p62
Ub
Ub
Ub
Ub
Ub
a.a.
lipids
Lyso
glucose
a.a.
ATROPHY