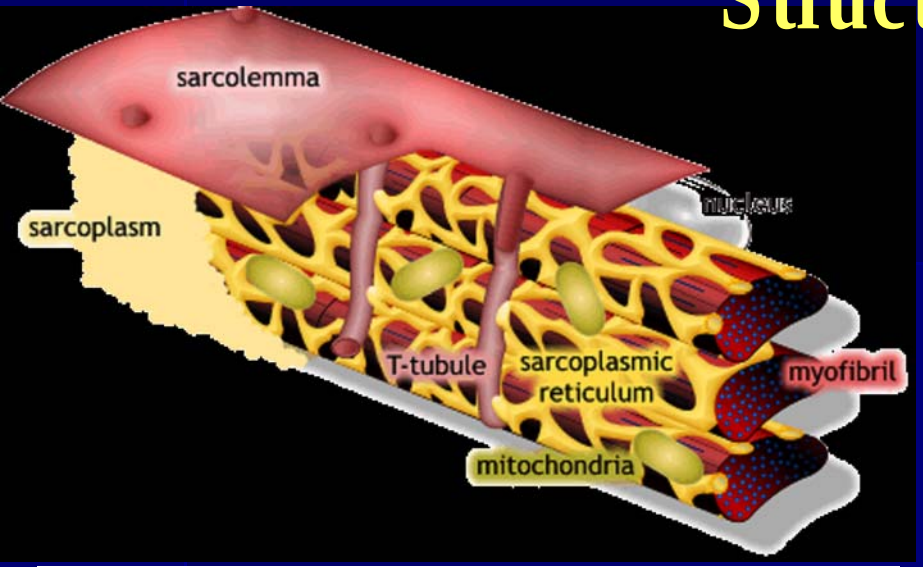
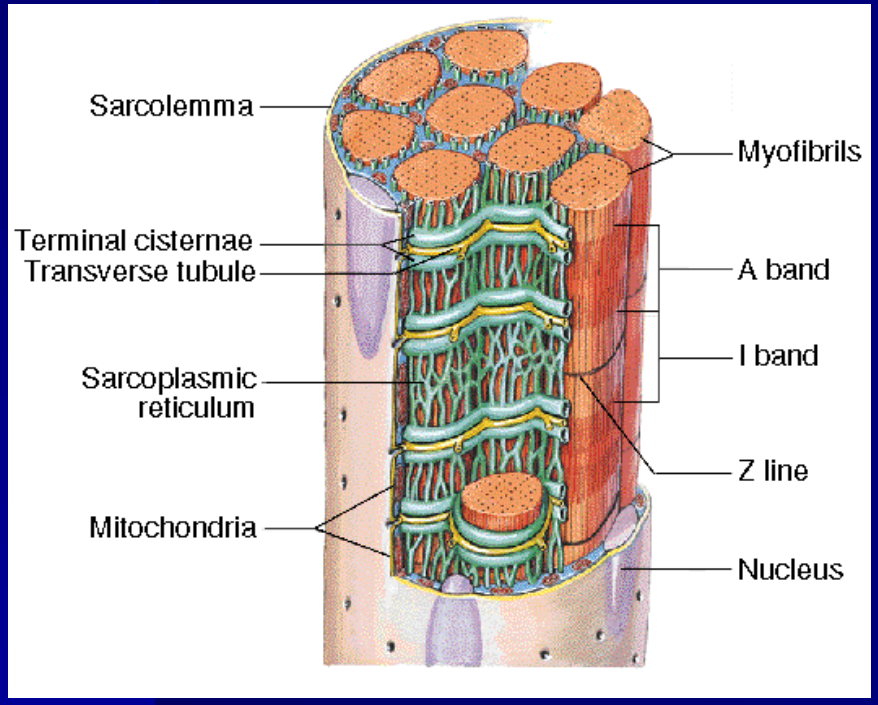
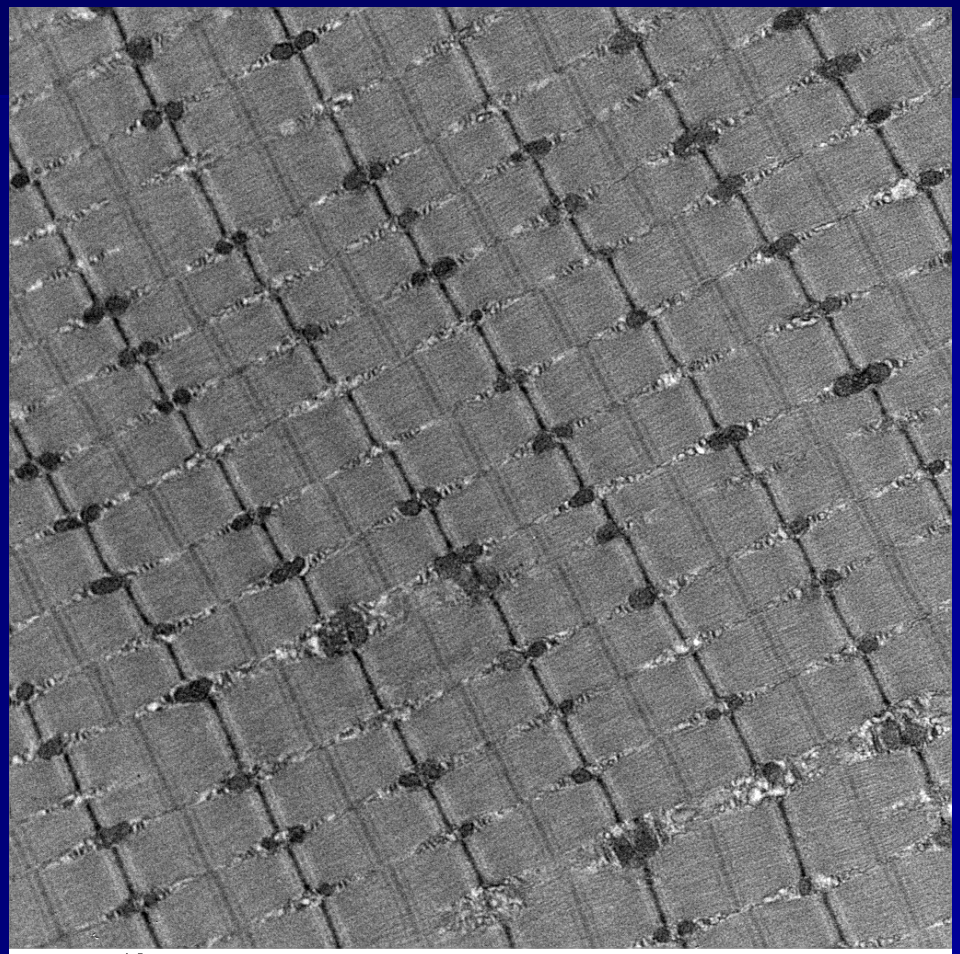
Signaling Pathways in Hypertrophy and Atrophy

Wook Song, Ph.D.
Exercise Physiology Laboratory
Seoul National University

Structure of Skeletal Muscle





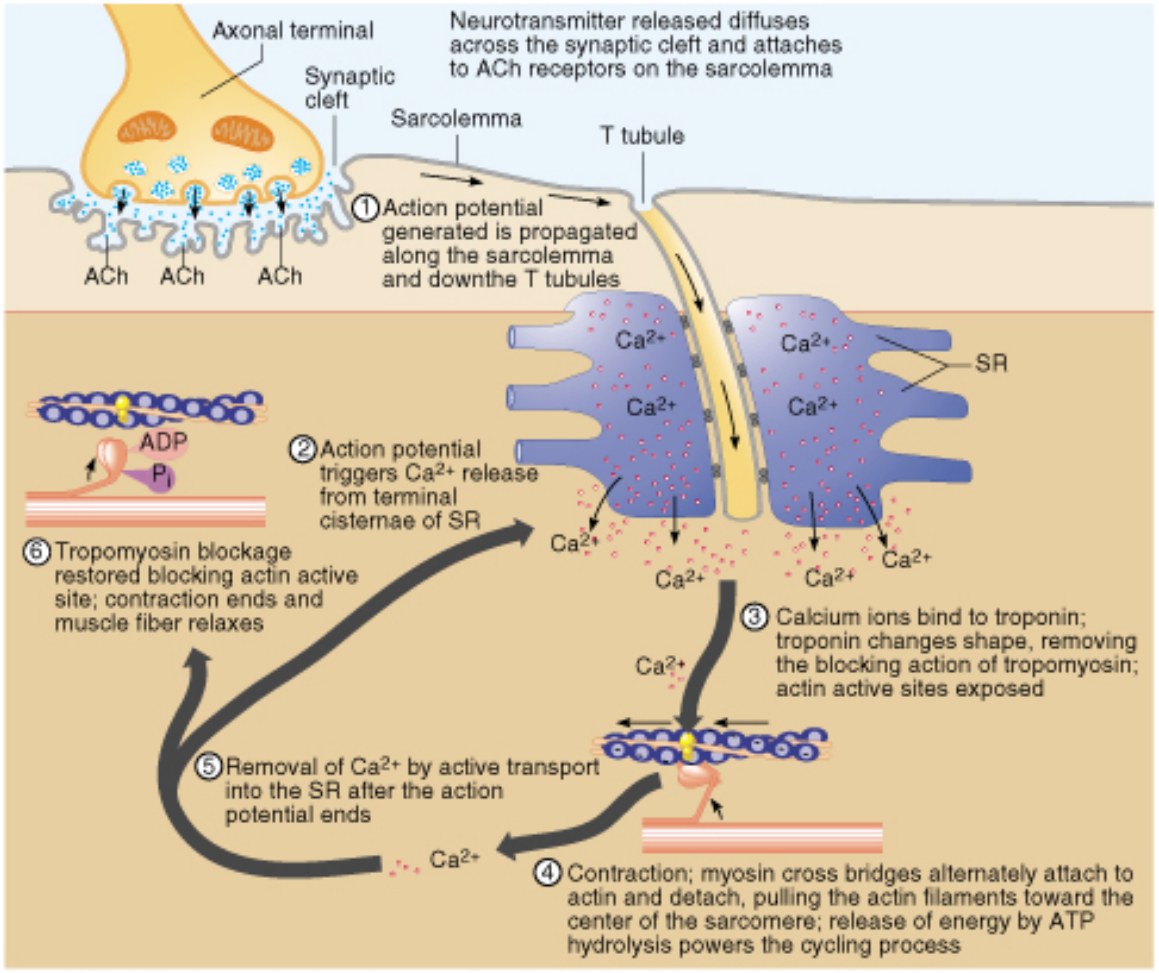


SONG_135.tif
WT_31mon
Print Mag: 15500x @ 8. in
10:07 03/15/05
Microscopist: BH

2 microns
HV=80kV
Direct Mag: 10000x
UTHSC-SA Pathology

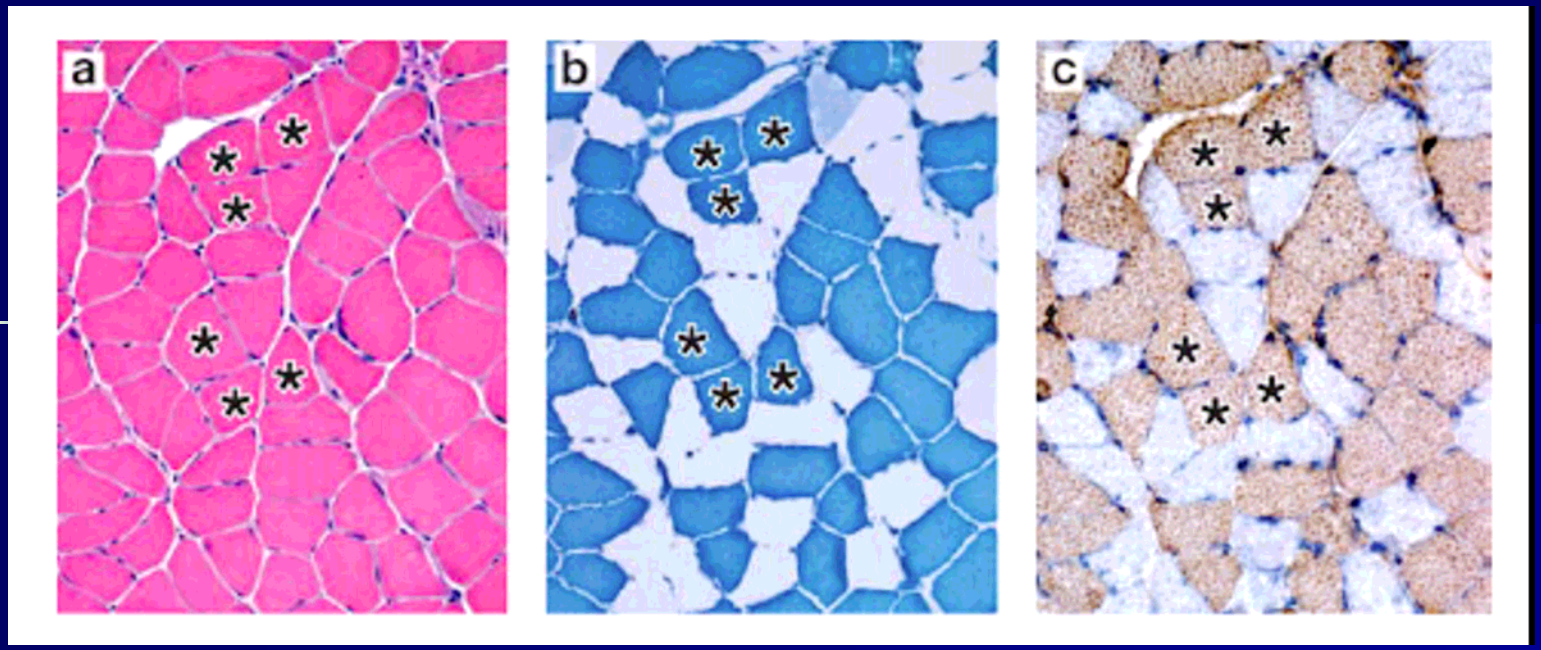
Function of Skeletal Muscle

: Contraction (Excitation-Contraction Coupling)



Diversity of Muscle fiber

Muscle fibers appears uniform histologically
But they are heterogenous with respect to size, metabolism, and contractile function



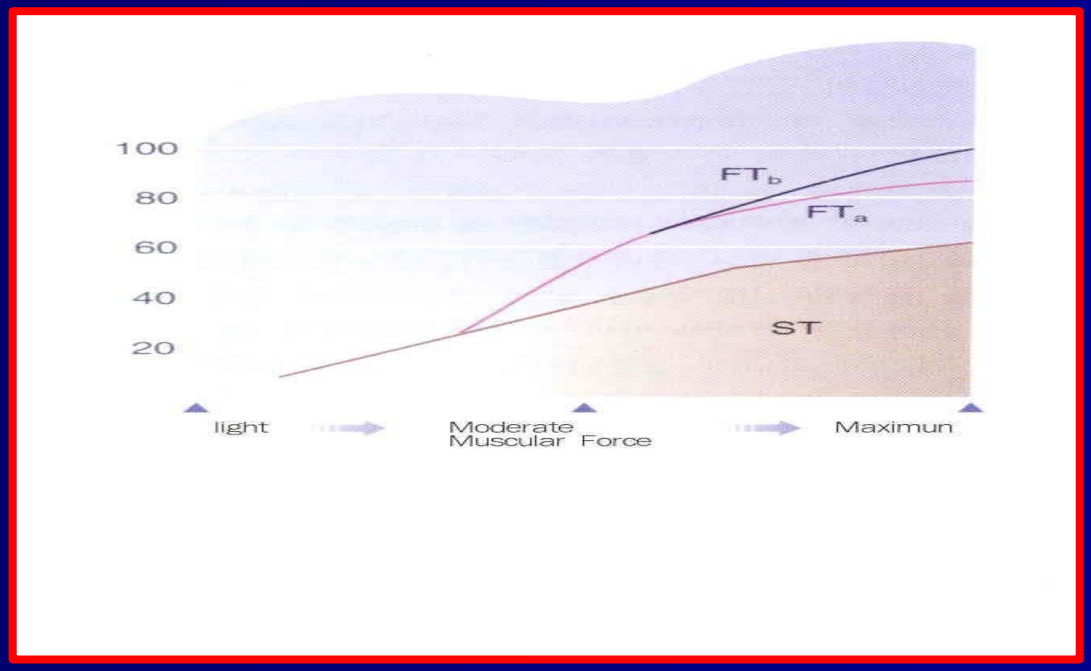
H&E (hematoxylin and eosin staining

Metachromatic dye-ATPase method
Dark blue→type I
Light blue→type IIA

Immunohistochemistry using a monoclonal antibody recognized type I myosin heavy chain

Annu.Rev.Biochem.

Muscle Fiber Recruitment by Size Principle



Wilmore & Costill, 2001

Size Principle

: In a steady contraction, small motor units (ST, type I) are recruited before larger ones (FT, type II)

Skeletal Muscle has a remodeling capacity (adaptation)

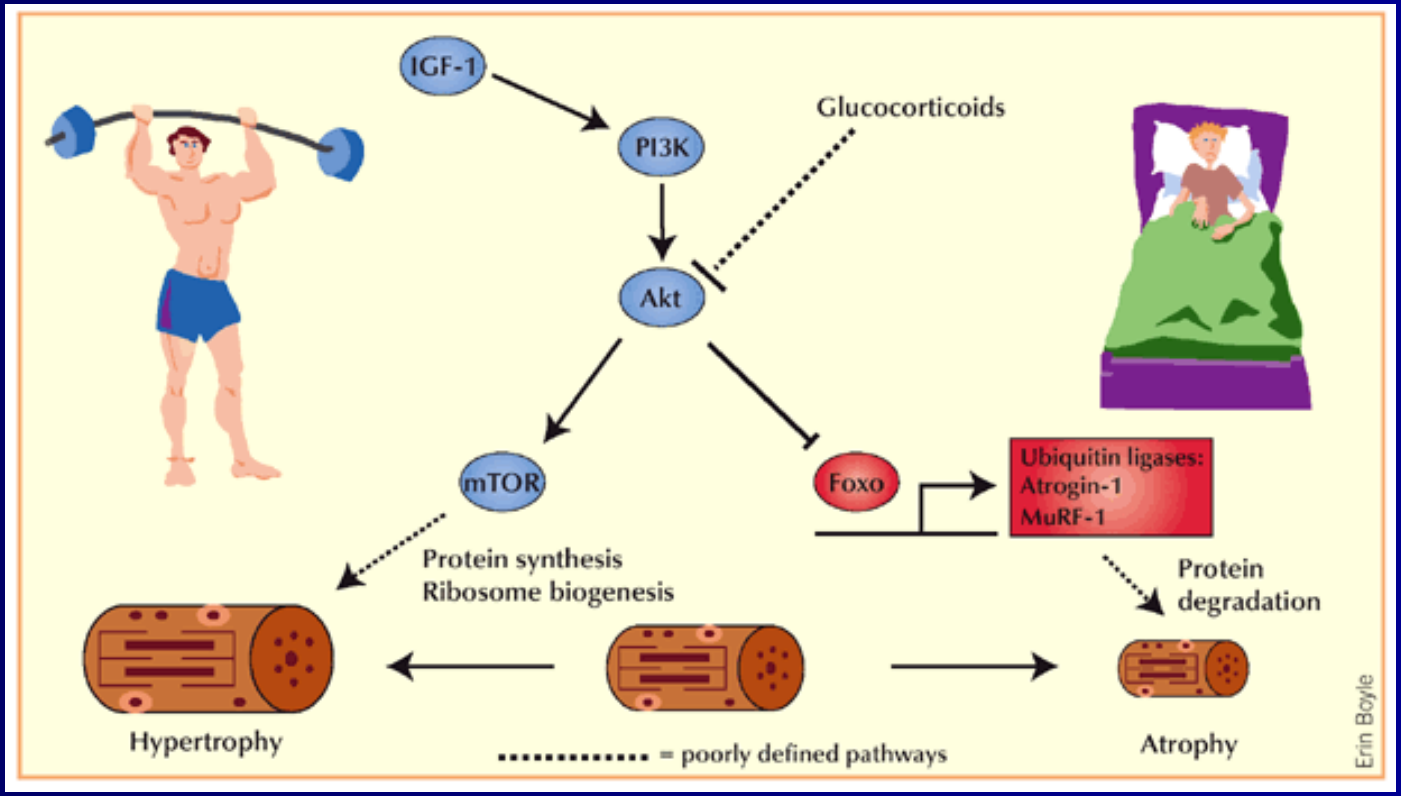
Skeletal muscle is comprised of heterogeneous myofibers that enables different muscle groups to fulfill a variety of functions

In response to environmental demands, skeletal muscle remodels by activating signaling pathways

Skeletal Muscle Adaptation

Increased Use	Decreased Use
Exercise	Immobilization
Chronic Electrical Stimulation	Spinal Cord Transection
Intermittent Electrical Stimulation	Hindlimb Unloading (Microgravity)
Chronic Stretch	Aging
	Denervation

Signaling Pathways in Skeletal Muscle Hypertrophy and Atrophy



Nature Med. 2004, 10(6):584–5

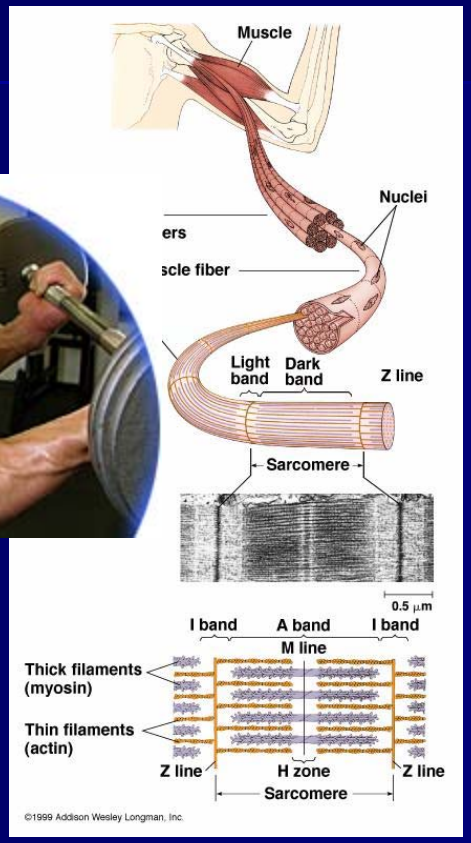
Major References (Review)

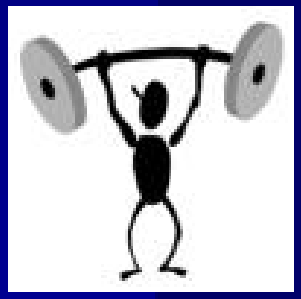
Nature Cell Biol. 5(2):87-90, 2003
Int J Biochem Cell Biol. 37(10):1985-96, 2005
Trends in Molecular Medicine. Vol 9 No.8, 2003
Int J Biochem Cell Biol. 37(10):1974-1984, 2005
Annu Rev Biochem. 75:19-37, 2006
Scince's stke, 2004
Am J Physiol Cell Physiol. 287:C834-43, 2004

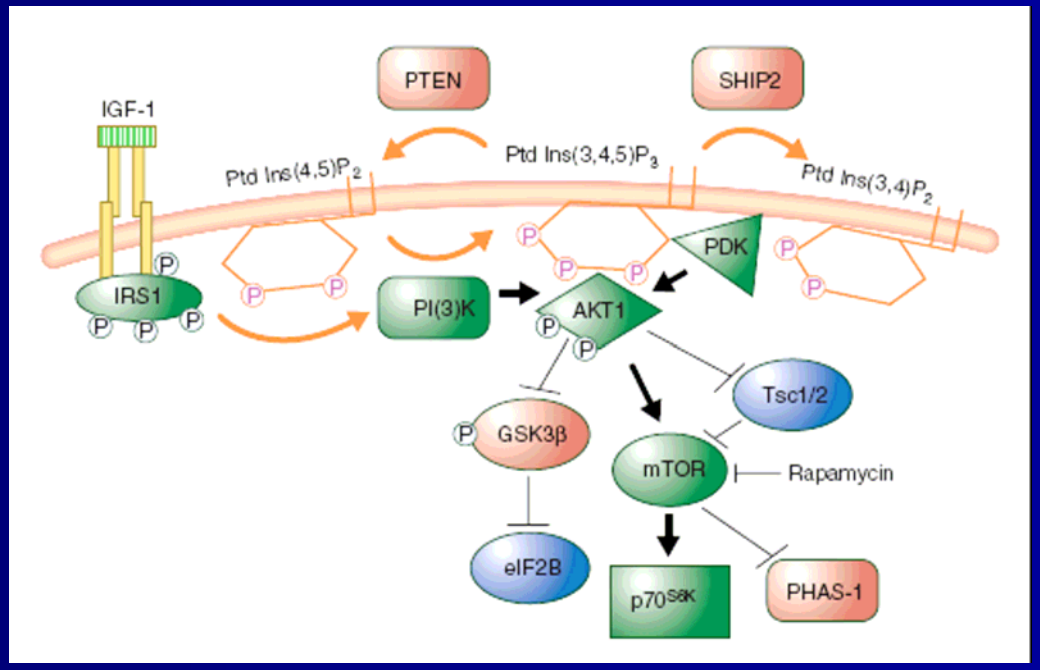
Terminology in Hypertrophy Signaling

IGF-1: Insulin-like Growth Factor-1
PI3K: Phophatidylinositol-3 Kinase
Akt
mTOR: mammalian Target Of Rapamycin
p70S6K

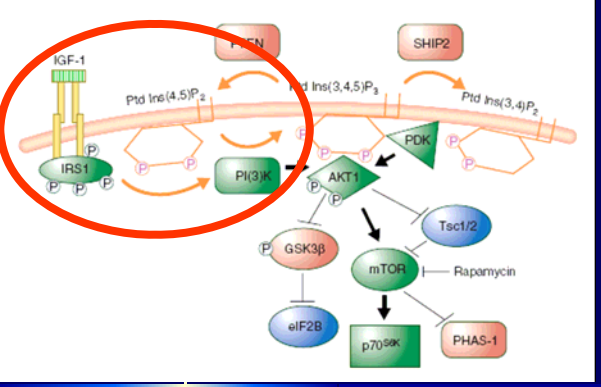
Hypertrophy Signaling Pathways







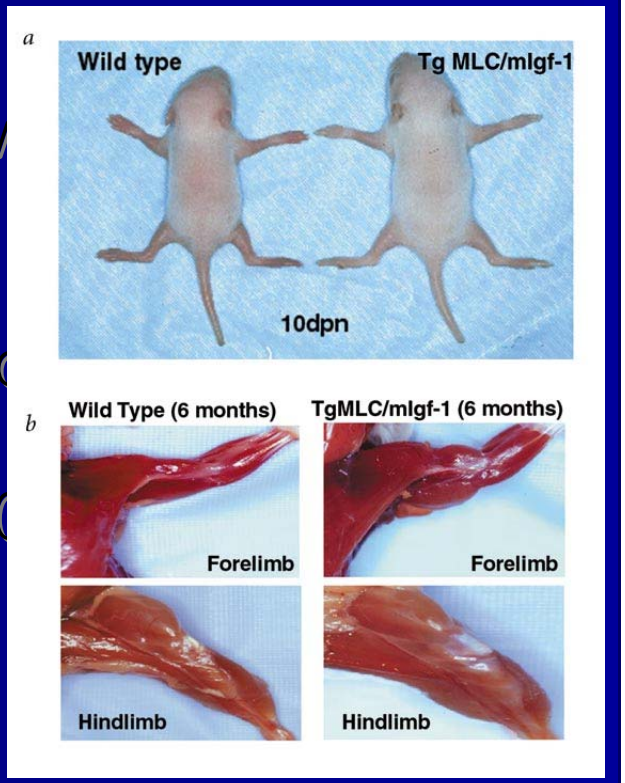
Nature Cell Biology, 2003



Hypertrophy Signaling
: The IGF-1/PI(3)K Pathway

Muscle expression of IGF-1 is sufficient to induce hypertrophy of skeletal muscle (*Natu Genet*, 2001)

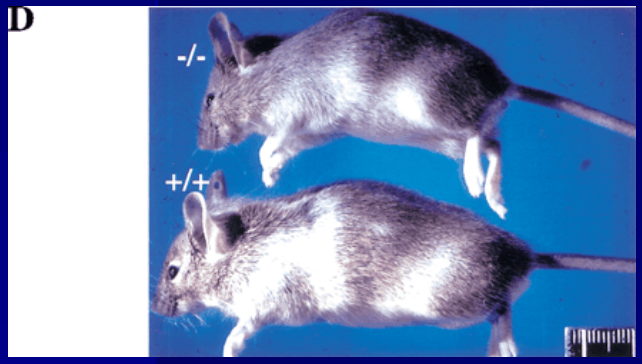
Activation of the PI(3)K pathway is implicate as a potential mediator of skeletal muscle hypertrophy via IGF-1 (*Nature Cell Biol*, 200



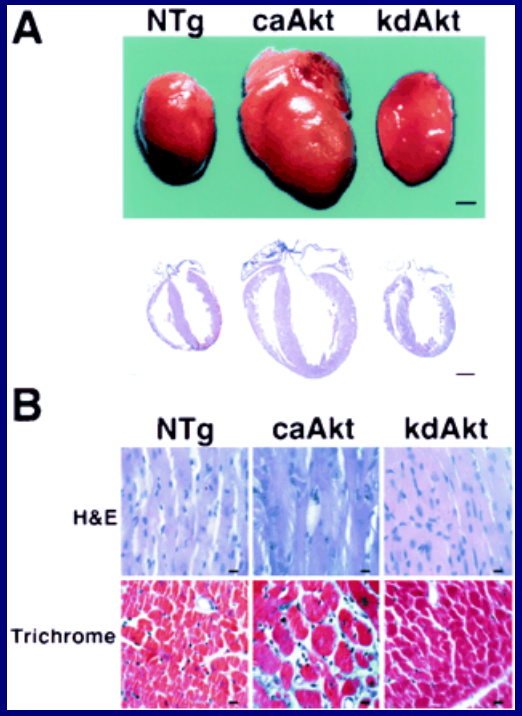
Nature Genet, 2001

Hypertrophy Signaling
: The PI(3)K/Akt Pathway

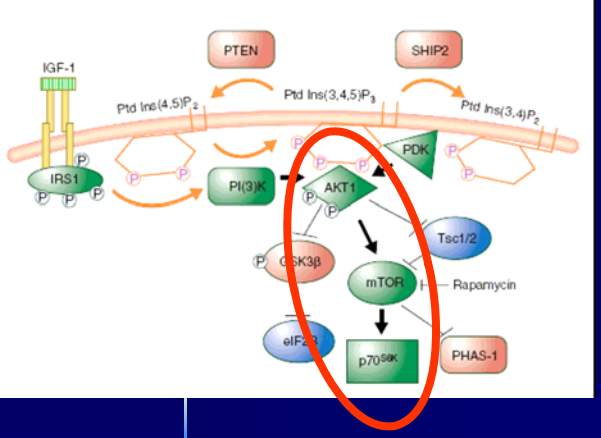
Akt1 activity is required for IGF-1 mediated hypertrophy, and expression of activated Akt1 is sufficient to induce muscle hypertrophy (*Science*, 1999, *Nature Cell Biol*, 2001)



Akt1$^{-/-}$ are smaller than WT demonstrating that Akt1 is required for normal organ growth (*Genes Dev*, 2001)

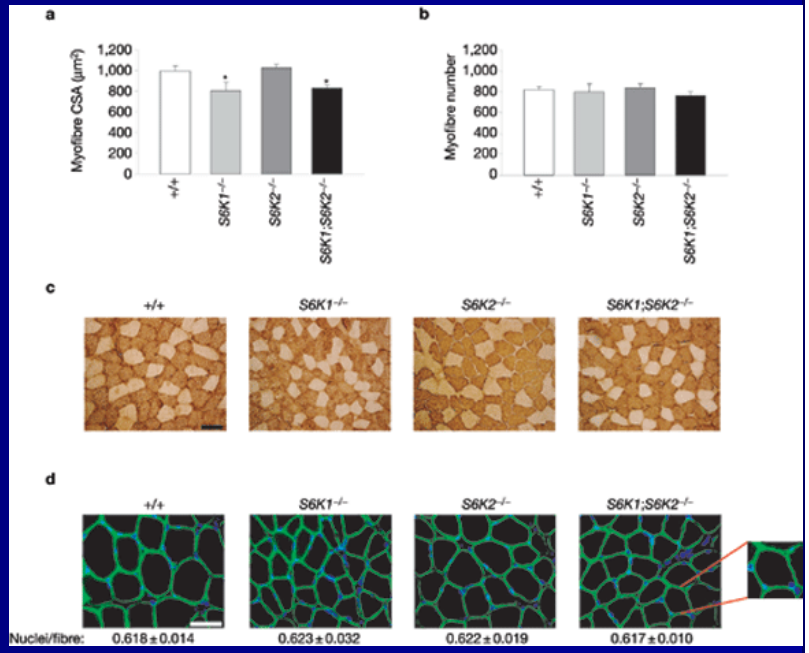


Transgenic mice that express a mutant, constitutively active form of Akt1 in cardiac muscle have hypertrophic hearts (*Mol Cell Biol*, 2002)



Hypertrophy Signaling
: The Akt/mTOR Pathway

Once Akt1 is activated, it initiates a cascade of phosphorylation events targeting mammalian target of rapamycin (mTOR) (*Biochem J*, 1999) mTOR can induce hypertrophy by modulating two distinct pathways including the p70S6K pathway. Activation of p70S6 kinase is necessary for muscle fibers to achieve normal size (*Nature Cell Biol*, 2005)



Atrophy of *S6K1-/-* skeletal muscle cells reveals distinct mTOR effectors for cell cycle and size control (*Nature Cell Biol*, *2005*)

Terminology in Muscle Atrophy Signaling

FOXO
MuRF1: Muscle Ring Finger protein1
MAFbx: Muscle Atrophy F-box (also called Atrogin-1)
Ubiquitin-proteasome system
Calpain (calcium-dependent)
Lysosomal proteases (i.e., cathesins)

Atrophy is not simply the converse of hypertrophy

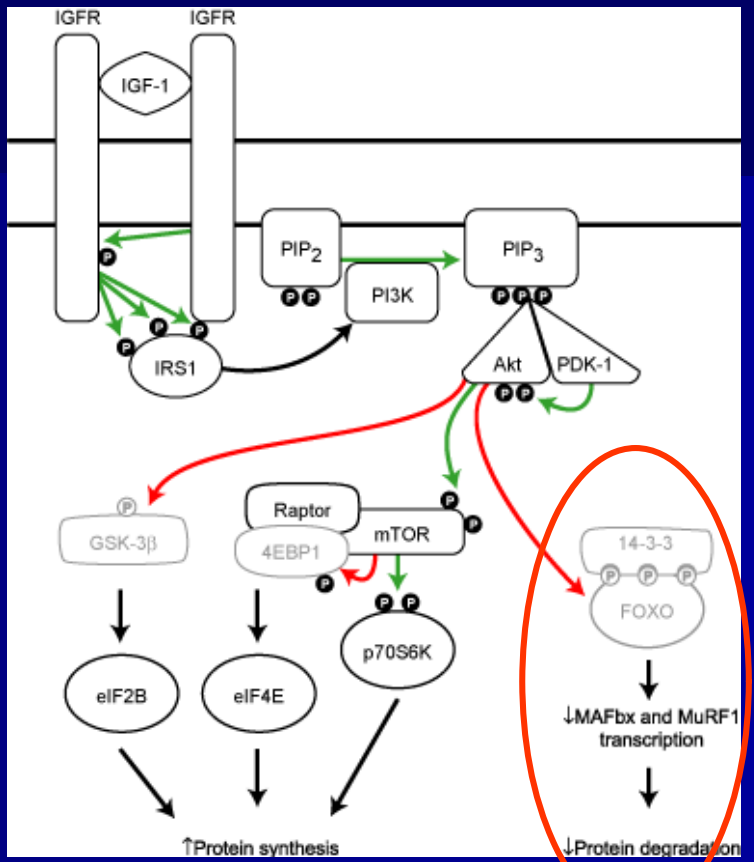
Establishment of an active transcriptional program is necessary for the induction of muscle atrophy

The FOXO transcription factors regulates atrophy by modulating MuRF1 and MAFbx

The ubiquitin protein ligases MuRF1 and MAFbx

MuRF1(Muscle RING Finger 1)

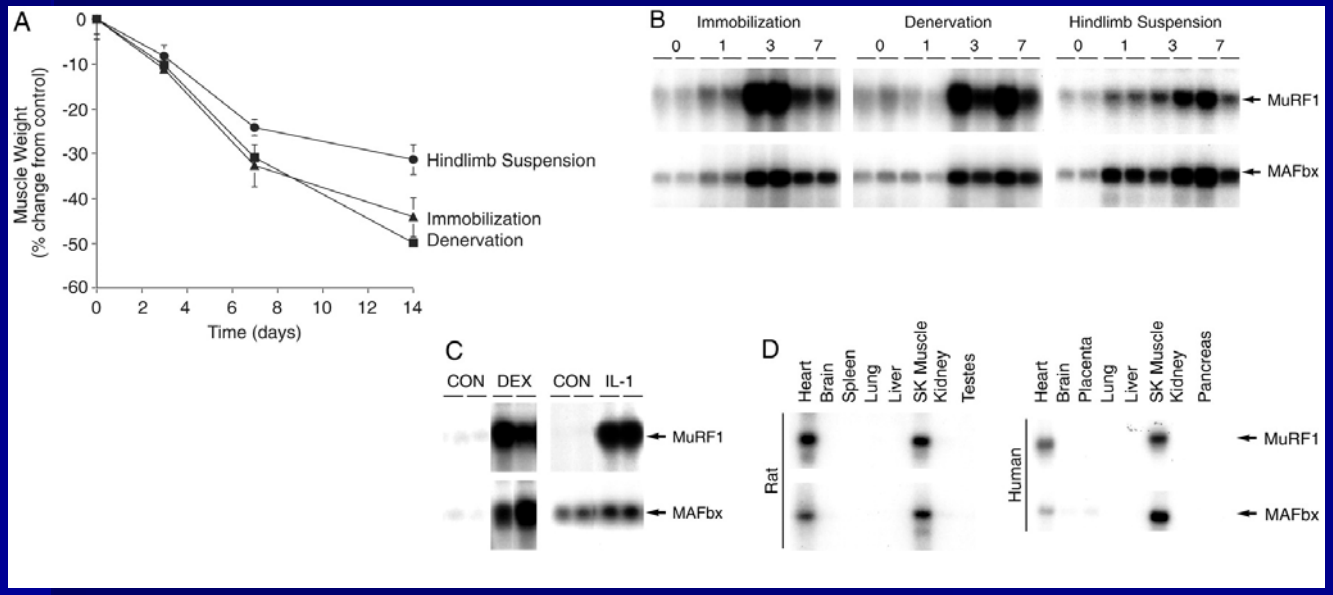
MAFbx(Muscle Atrophy F-box; also known as atrogin-1)



Akt negatively regulates FOXO transcription factors by phosphorylating

MuRF and MAFbx up-regulated in numerous atrophy models

Expressed specifically in skeletal and cardiac muscle
Two genes (MuRF & MAFbx) are up-regulated in multiple models of skeletal muscle atrophy (i.e., sepsis, cachexia, denervation, hindlimb suspension and immobilization etc)



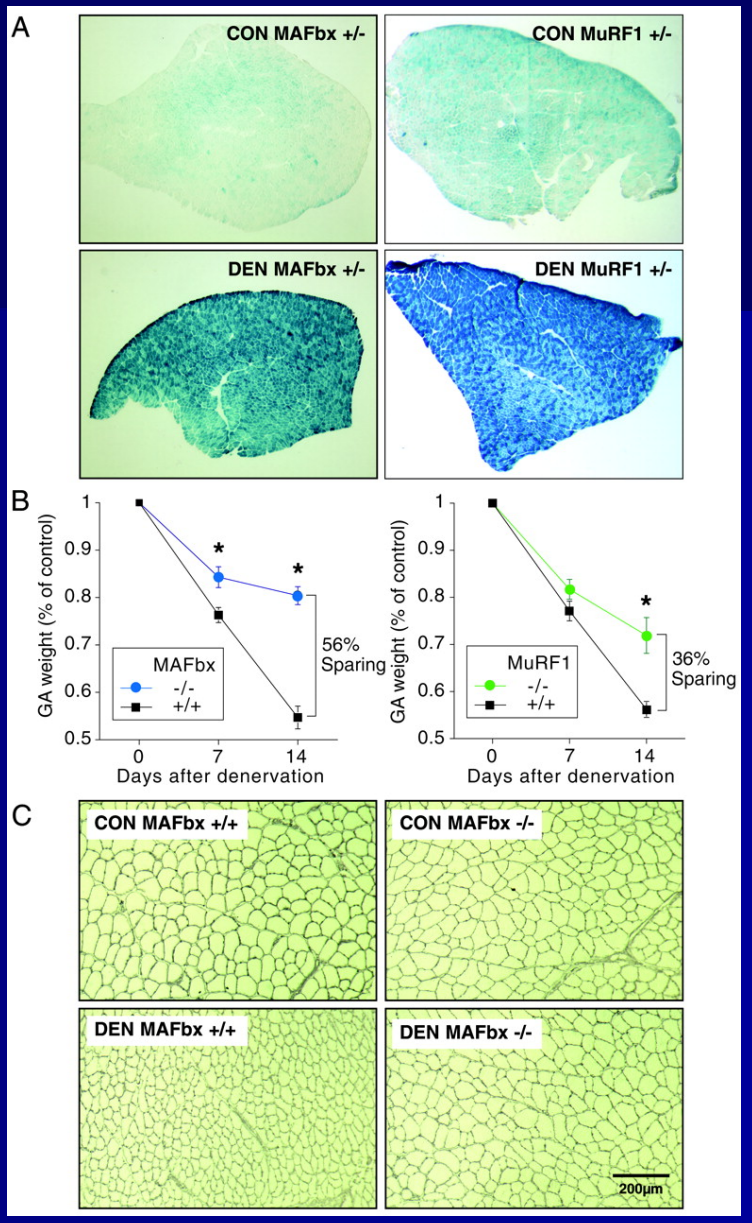
Science, 2001

MuRF1 or MAFbx as a marker of skeletal muscle atrophy?

MuRF1$^{-/-}$ and *MAFbx*$^{-/-}$ mice appear phenotypically normal. However, under atrophy conditions, significantly less muscle is lost in either *MuRF1*$^{-/-}$ and *MAFbx*$^{-/-}$ mice (*Science*, 2001)

MuRF1 or MAFbx might be **attractive targets for pharmacological intervention**

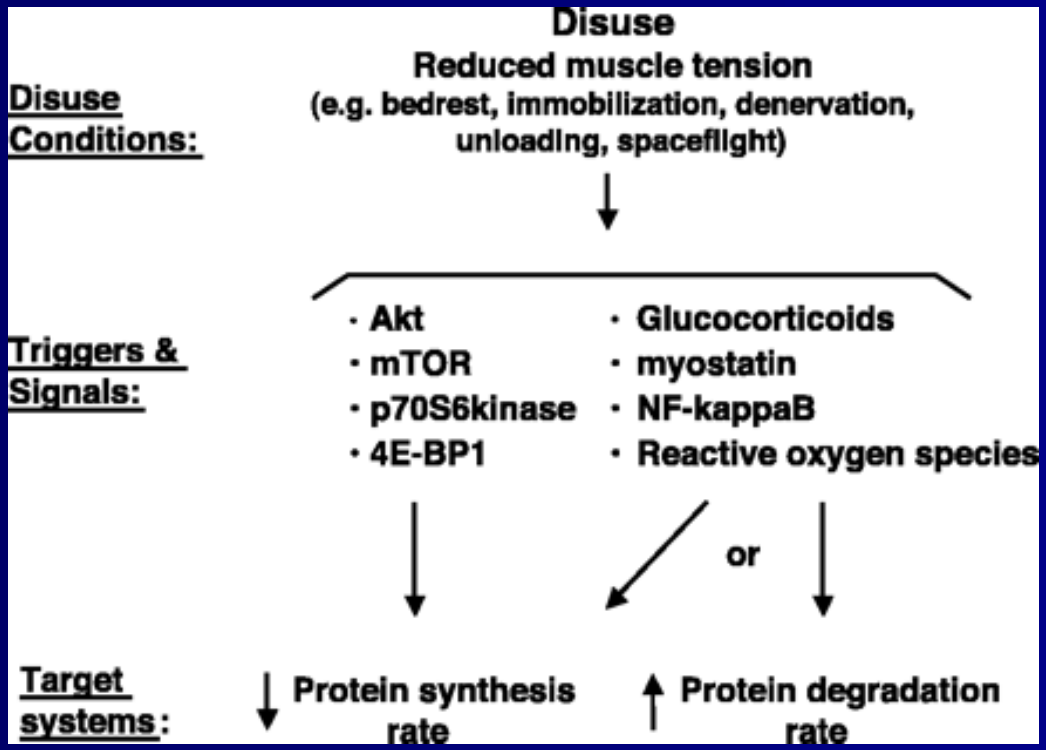
MuRF1 or MAFbx might serve as **early makers of skeletal muscle atrophy** aiding in the diagnosis of muscle disease



Science, 2001

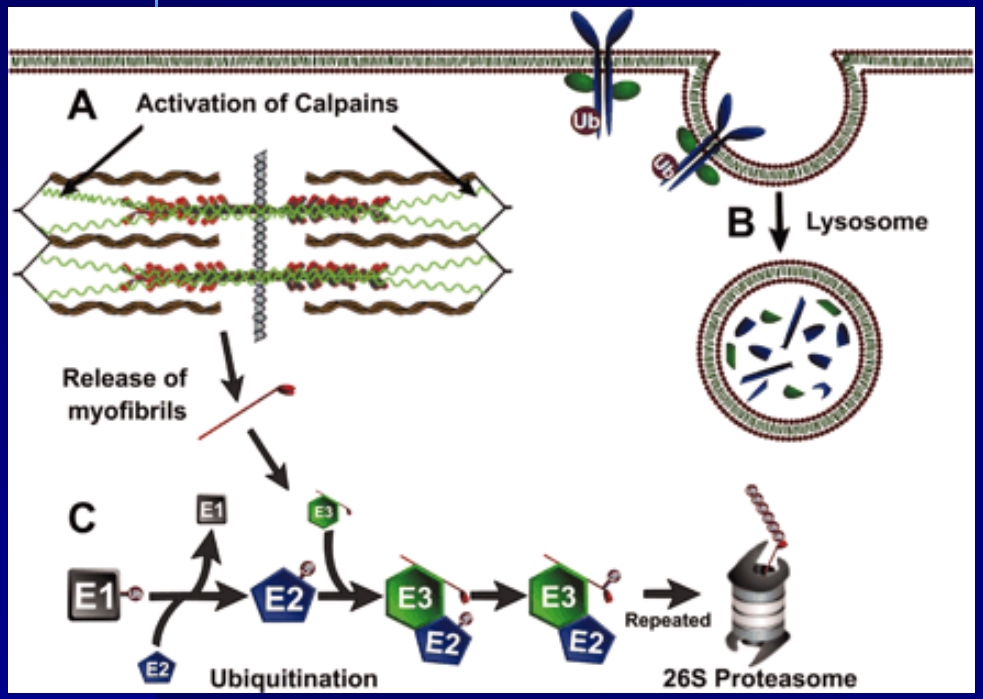
Molecular Basis of Muscle Atrophy

There are many of molecular triggers and signals that have been implicated in muscle atrophy



AJP–Cell Physiol, 2004

Proteolytic systems implicated in skeletal muscle atrophy

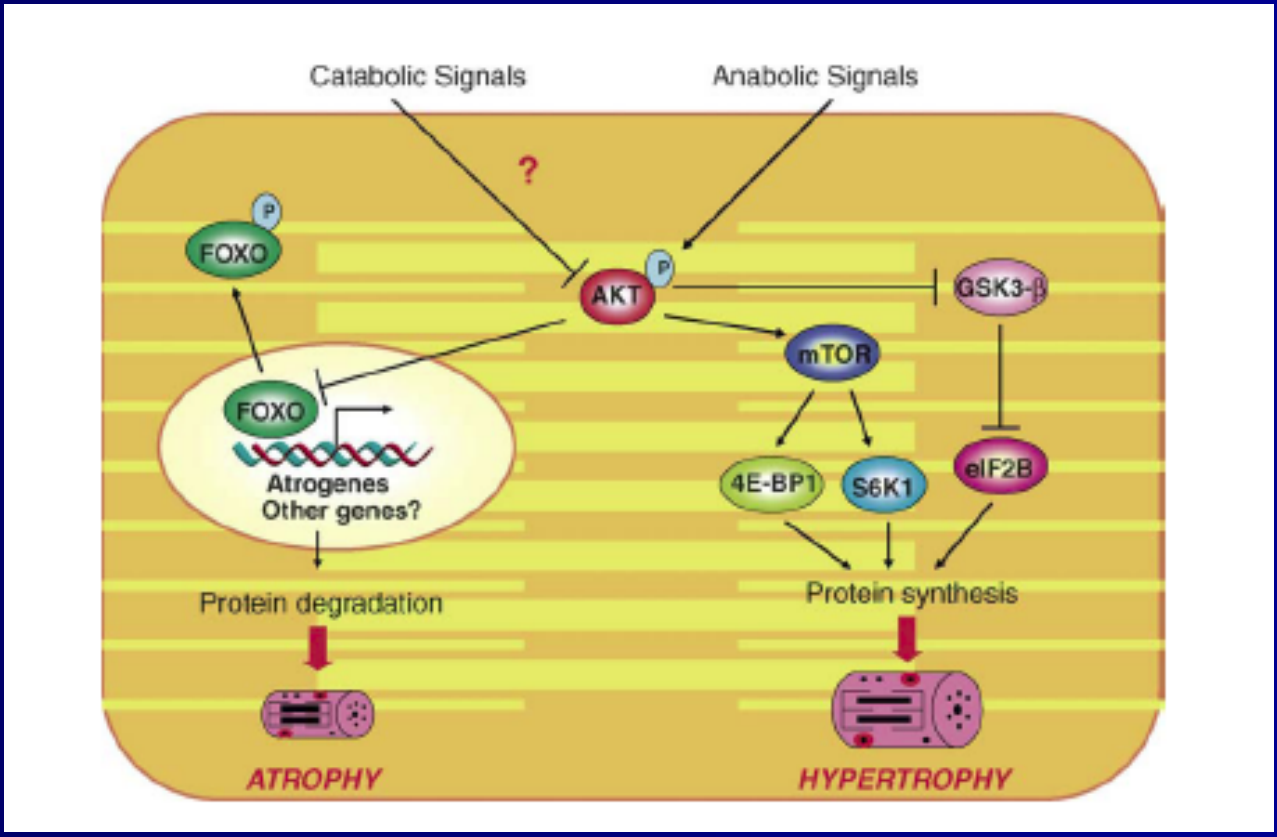


AJP-Cell Physiol, 2004

A. Calcium-dependent calpain system
B. Lysosomal protease system (cathepsins)
C. Ubiquitin-proteasome system

Recent evidence points toward interactive involvement of these 3 systems in proteolysis

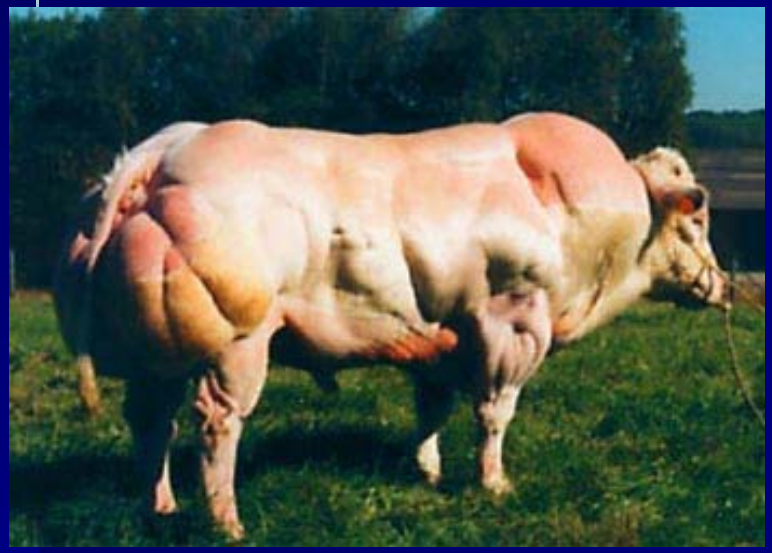
AKT signaling network during hypertrophy and atrophy



Intl J Biochem Cell Biol, 2005

Myostatin

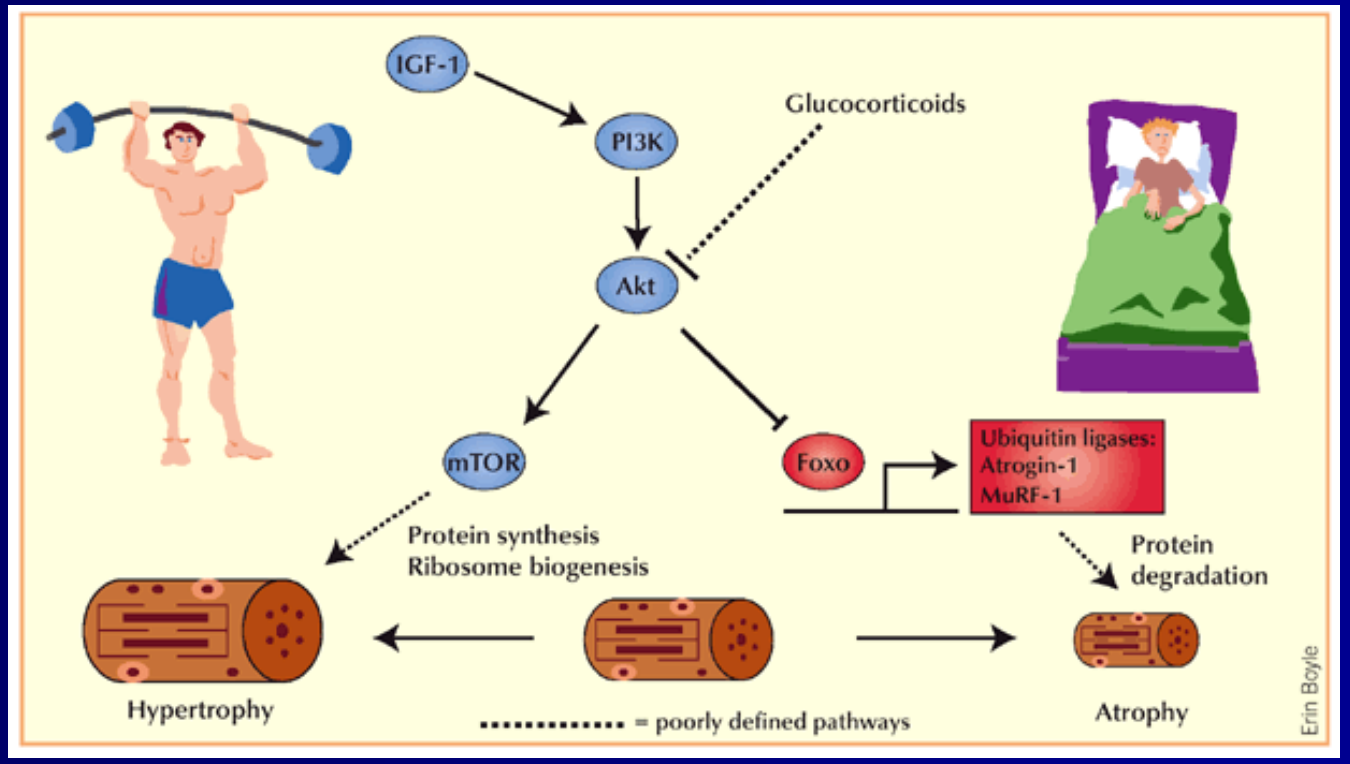
Negative regulator of skeletal muscle growth



A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle (*Nature Genet, 1997*)

A fullblood Belgian Blue bull showing the double muscling phenotype (*PNAS, 1997*)

Signaling Pathways in Skeletal Muscle Hypertrophy and Atrophy



Nature Med. 2004, 10(6):584–5

SUMMARY

Molecular mediators of hypertrophy and atrophy in skeletal muscle have only recently begun to be determined.
Genetic and pharmacological modulation of skeletal muscle signaling pathways offer therapeutic opportunities for the treatment of muscle diseases.
In the future, exercising might mean taking a "pill" to activate skeletal muscle remodeling via signaling pathways. *But for now, it is no pain, no gain. Keep on running.*

Future Issues To Be Resolved

Confirmation is needed to determine whether signaling pathways are physiologically valid and are involved in humans.

It remains unclear many signaling pathways are initiated by the motor neuron and how the pathways are intercalated.

The identity of additional transcription factors and target genes that are involved in skeletal muscle remodeling remains to be determined.