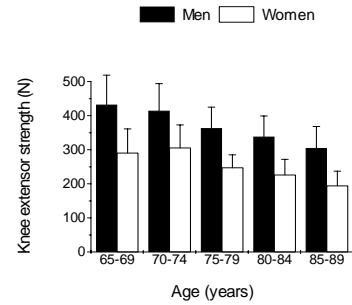


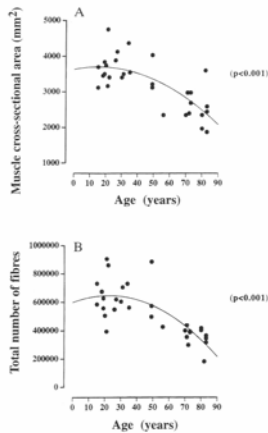


Role of local growth factors in the maintenance of muscle mass in older people.



Skelton *et al.* (1994)
 Age & Ageing 23: 371-377

Loss of muscle fibres with increasing age



Lexell *et al.* (1988)
 J Neurol Sci 84: 275-94

Ageing is associated with selective fast fibre atrophy

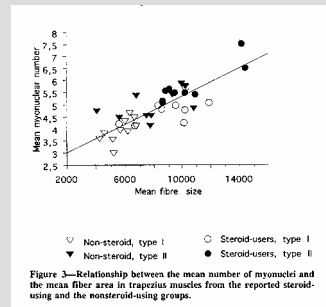
Mean fibre CSA (μm^2)

	Type I	Type IIa
Young (20-30 years)	4500	5000
Old (70 years)	4400	3000*

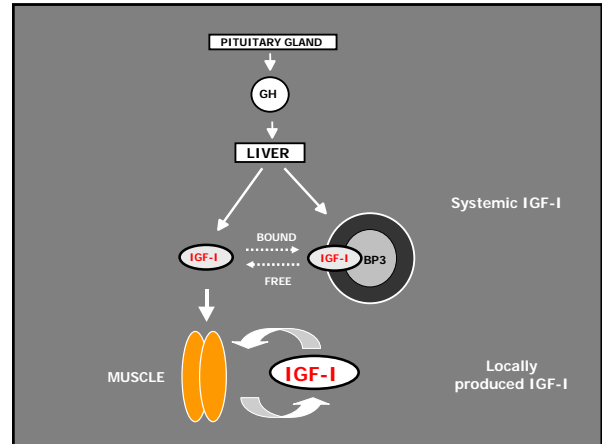
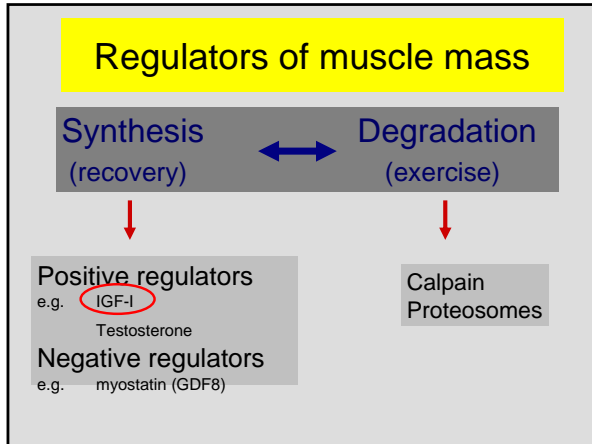
Klitgaard *et al.* (1990)
 Acta Physiol Scand 140:41-54

Basic requirements for muscle growth

- Net gain in protein
- Provision of new nuclei



Kadi *et al.* (1999)
 MSSE 31, 1528-1534



Manipulation of local IGF-1 expression

Transgenic mouse
Over expression of IGF-1(Ea) in muscle

→ enhanced muscle mass

→ maintenance of mass in old age

Musaró *et al.* (2001)
Nature Genetics 27:195-200

Alternative Splicing of the Human IGF-I Gene

IGF-I: P1-1-P2-2-3-4-5-6

IGF-IEa: 3-4-6

IGF-IEc: 3-4-6

↑
49bp insert

hormones

mechanical signals?

Yang *et al.* (1996)
J Mus Res Cell Motil 17, 487-495

1 isoform in control muscle
2 isoforms in overloaded muscle

Alternative Splicing of the Human IGF-I Gene

IGF-I: P1-1-P2-2-3-4-5-6

IGF-IEa: 3-4-6

IGF-IEc (MGF): 3-4-6

↑
49bp insert

hormones

mechanical signals?

Yang *et al.* (1996)
J Mus Res Cell Motil 17, 487-495

1 isoform in control muscle
2 isoforms in overloaded muscle

MGF in soleus and plantaris of rats after 5 days of overload induced by tendon ablation

Age Group	Control	Overloaded
Young	~15	~155*
Mature	~30	~75*
Old	~10	~30*

Owino *et al.* (2001)
FEBS Lett. 505:259-263

What does resistance exercise do to IGF-I isoform expression in human muscle?

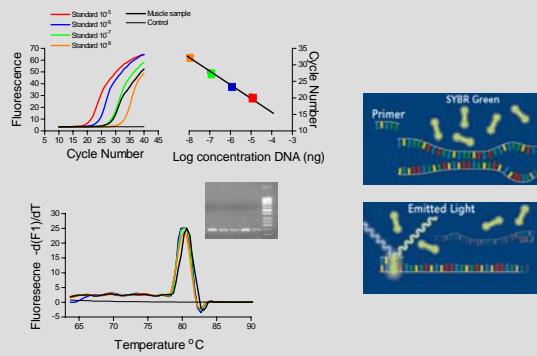
Hameed et al. (2003)
J. Physiol. 547: 247-254

MGF mRNA expression following an acute bout of resistance exercise

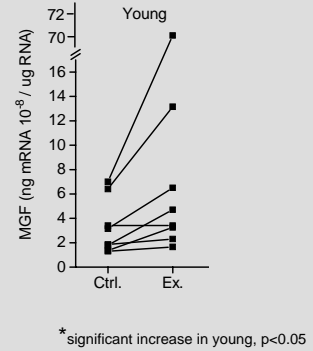
- **Subjects**
 - 8 young men (20 -35 yrs)
 - 7 older men (72- 80 yrs)
- **Exercise**
 - single legged knee extensor weightlifting
 - 10 x 6 x 80% 1-RM
- **Muscle sampling**
 - Needle biopsies control & exercised leg +2.5 hrs



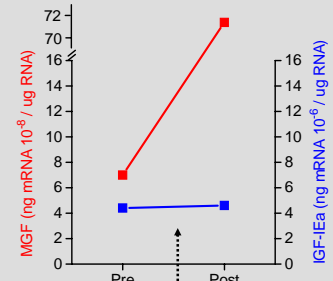
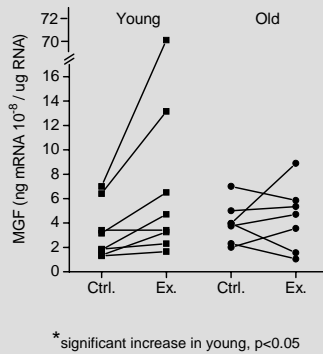
Quantification of IGF I mRNAs using real time PCR



MGF expression after weightlifting exercise



MGF expression after weightlifting exercise




So does this mean that older people cannot adapt to muscle strengthening exercise?

Effects of strength training in very elderly people

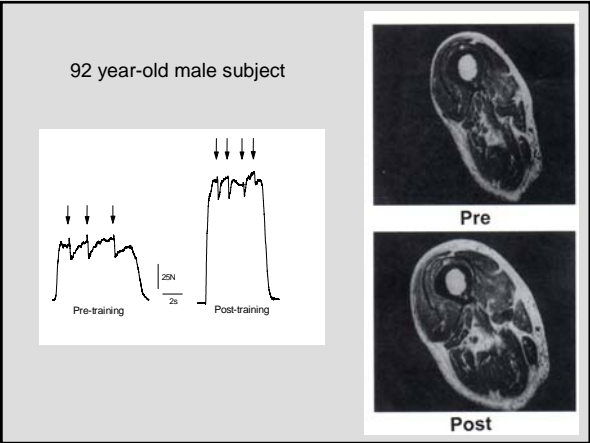
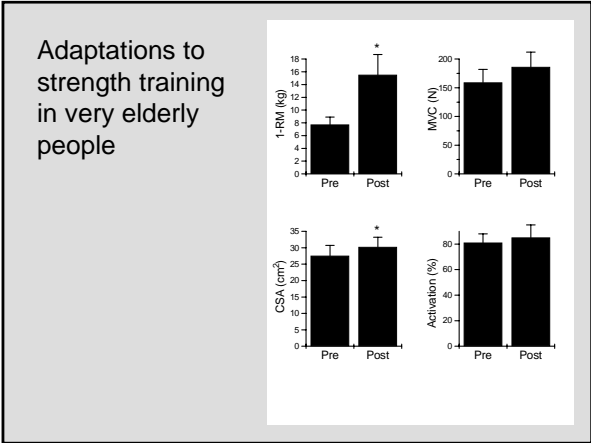
4 males 85 - 92 years
7 females 85 - 97 years

12 weeks - 3 times per week

3 x 6 x 80% 1-RM

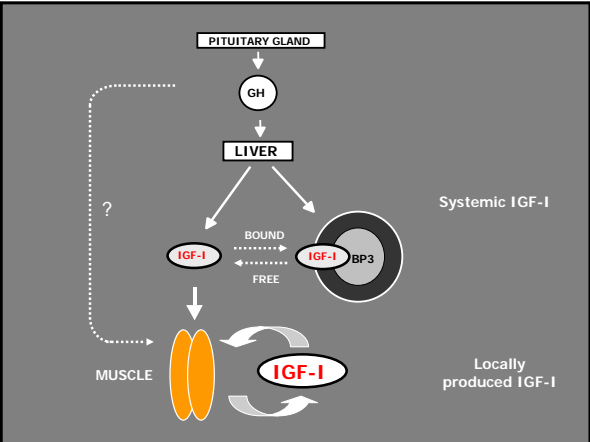


Harridge *et al.* (1999)
Muscle & Nerve 22:831-839



Effects strength training and growth hormone administration on IGF-1 isoform expression in older people

Hameed *et al.* (2004)
Lange *et al.* (2002)



Study Protocol

Subjects

- 19 healthy elderly men (70 ± 2yrs)

Groups - randomised

- Resistance training (n=6) – plus placebo
- Resistance training + GH (n=6) 0.5- 1.5 IU.m⁻²
- GH only (n=7) 0.5 – 1.5 IU.m⁻²

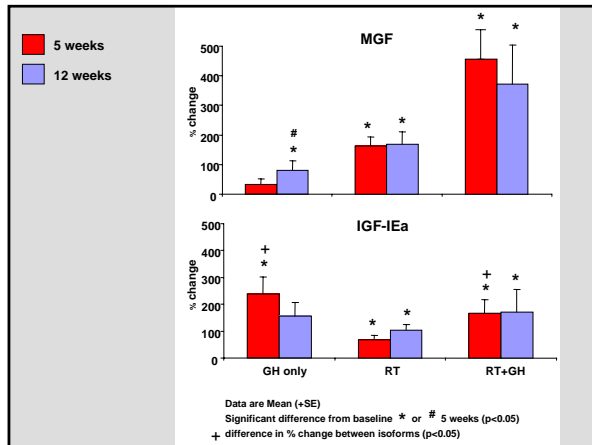
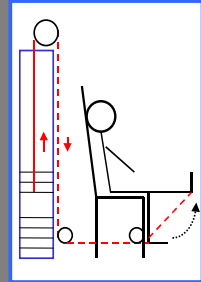
Study Protocol

Exercise

- Knee extensor weightlifting exercise
- 3 sessions / week
- 3-5 sets of 8-12 repetitions per session
- (60-70% 1- RM)

Muscle Sampling

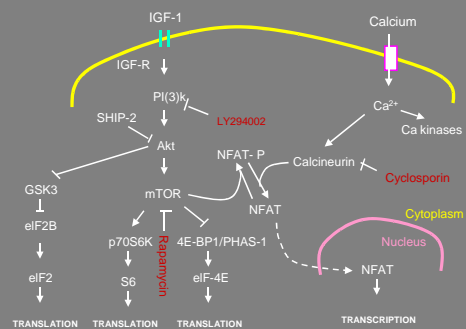
- Muscle biopsies pre, 5 and 12 wks
- 24 hours after last training session



So what does IGF-I do?

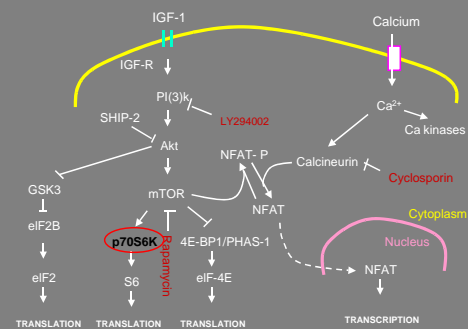
Do the different isoforms of IGF-I have different roles?

Stimulation of protein synthesis

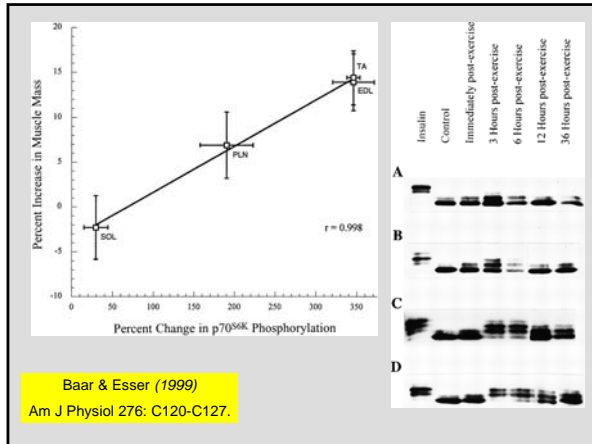


Rommel et al. (2001)
 Nature Cell Biol. 3:1009-1013

Stimulation of protein synthesis



Rommel et al. (2001)
 Nature Cell Biol. 3:1009-1013



Is the prime function of MGF to activate satellite cells?

A satellite cell (blue nucleus) adherent to a muscle fibre surface by the muscle-specific adhesion molecule, M-cadherin

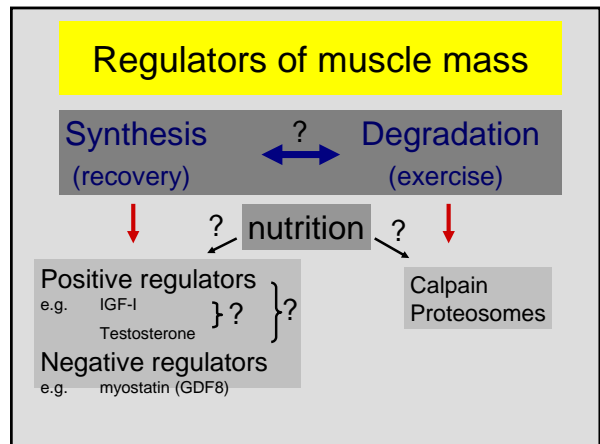
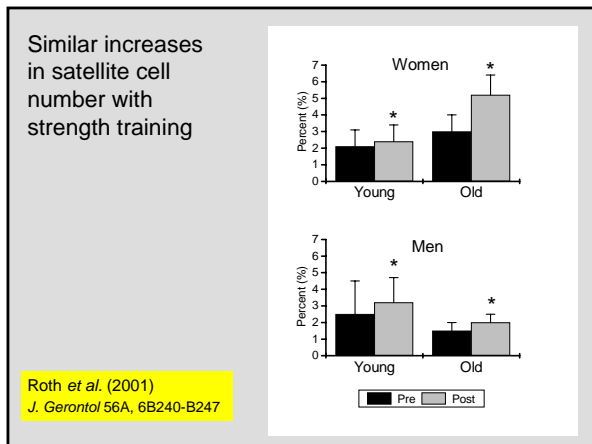
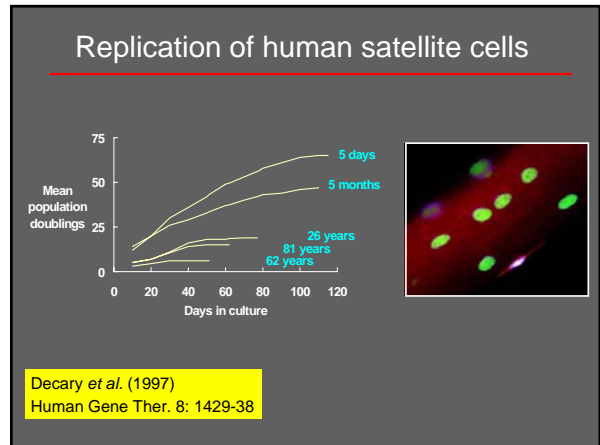
Partridge, T
Imperial College

Different affects of the two IGF-I isoforms on muscle cells in culture

Transfected C2C12 cells

MGF-positive	IGF-IEa -positive	Control C2C12 cells

Yang & Goldspink (2002)
FEBS Lett 522, 156-160



Summary

- Muscle adaptation to overload is regulated at a local level
- IGF I, a potent anabolic agent, is produced by the muscle itself for autocrine / paracrine actions
- The IGF I gene can be spliced to form different isoforms with different physiological functions
- The muscles of older people remain responsive to overload and can adapt to strength training exercise
- Adaptation is limited to the muscle fibres that still exist in the older muscle!

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