Understanding Soft Tissue Aging - the Effect of Cyclical Loading

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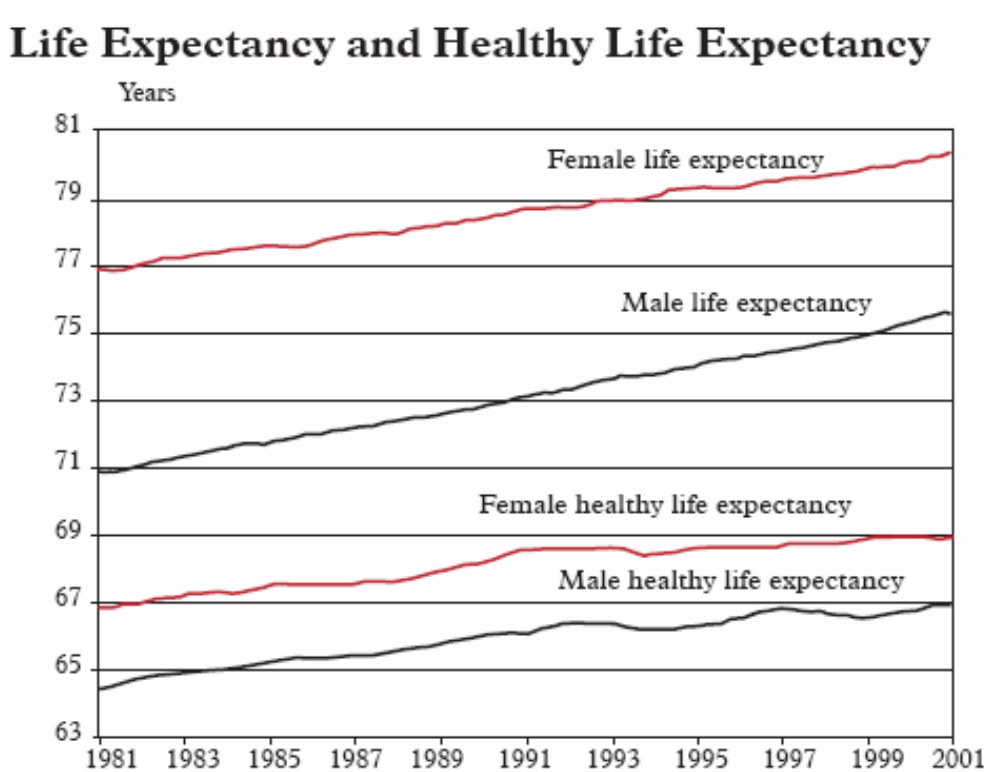
The importance of healthy living

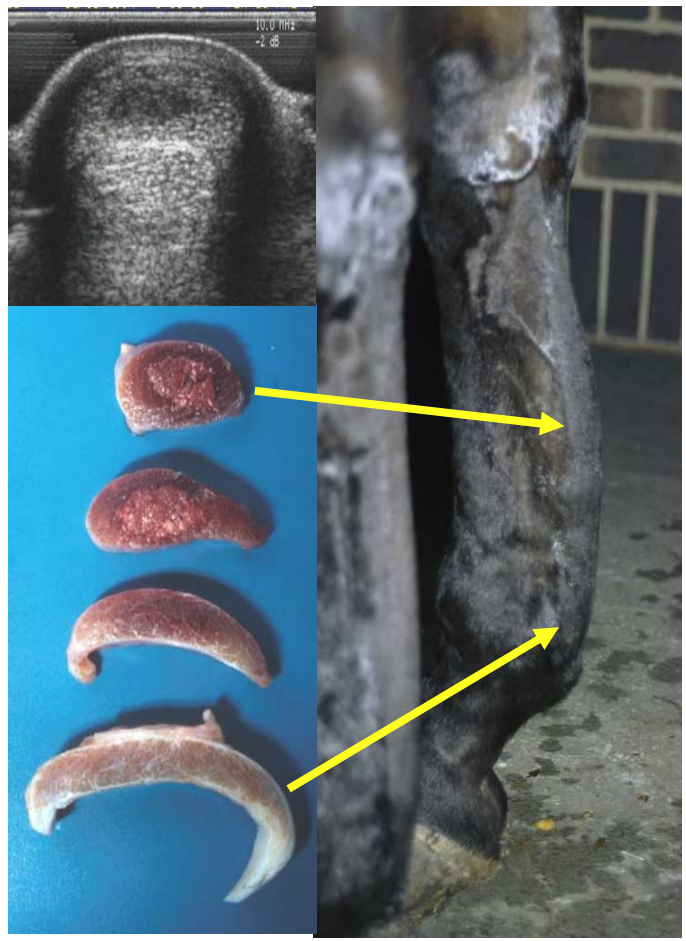
- Life expectancy is increasing but healthy life expectancy is 'levelling off'
- Greater importance of age-related diseases
  - Morbidity
  - Cost to health service
  - Need for prevention



'Aging: Scientific Aspects'; House of Lords, Science and Technology Committee, 2005

Strain-induced tendinopathy in humans and horses

- Very common in human and equine athletes
  - Many similarities
- Achilles tendinopathy in humans
  - increasing prevalence (Moller et al. 1996; Houshian et al. 1998; Maffulli et al. 1999)
- Superficial digital flexor tendinopathy in horses
  - Up to 43% of NH horses in training
  - 46% of limb injuries at racecourses
- Healing slow and poor
  - Re-injury common
  - Morbidity

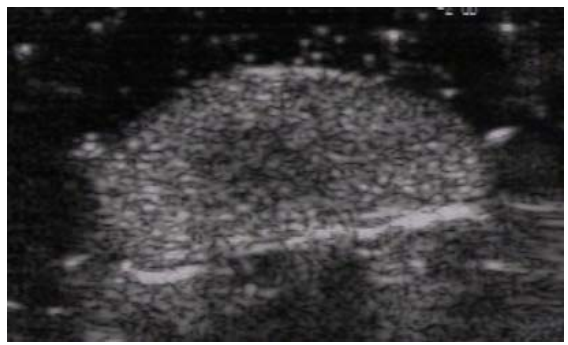


Why do tendons fail?

- High risk tendons operating close to functional limit
- Cause of injury
  - Sudden over-extension
  - Preceding tendon degeneration

Evidence for preceding degeneration

- 'Asymptomatic' lesions at post mortem
  - Webbon 1977, Goodship et al. 1994, Kannus and Jozsa 1991, Riley et al. 1994
- Bilateral nature of injuries
- Strong relationship between age and injury
- Aging induces a decline in mechanical competence
  - Onambele et al. 2006
- Cyclical loading *in vivo* drives cumulative fatigue damage in experimental exercise studies in the adult horse

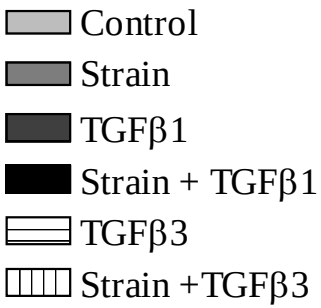


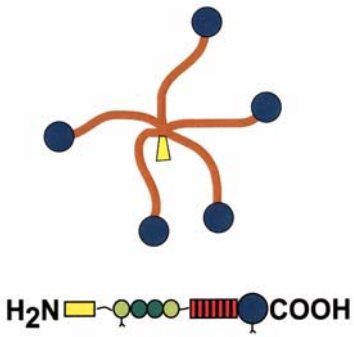
Tendon degeneration – an inevitable consequence of aging and exercise

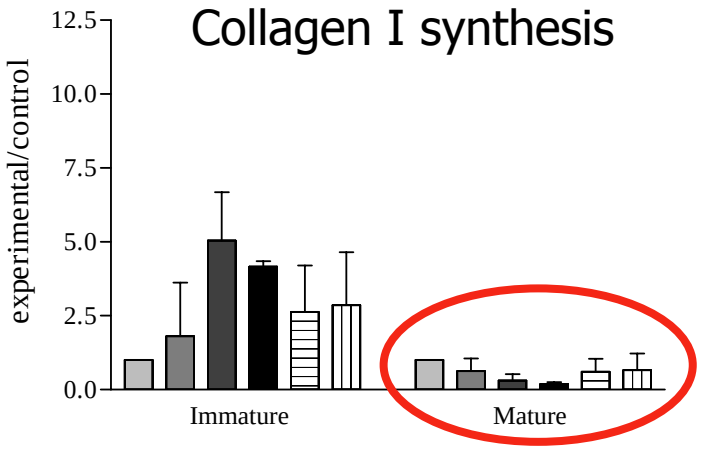
- Prevention strategies
  - Starting training early – tendon adaptive
    - Reduces risk of injury in racehorses
  - Post skeletal maturity - reduced degeneration will reduce risk of tendinopathy

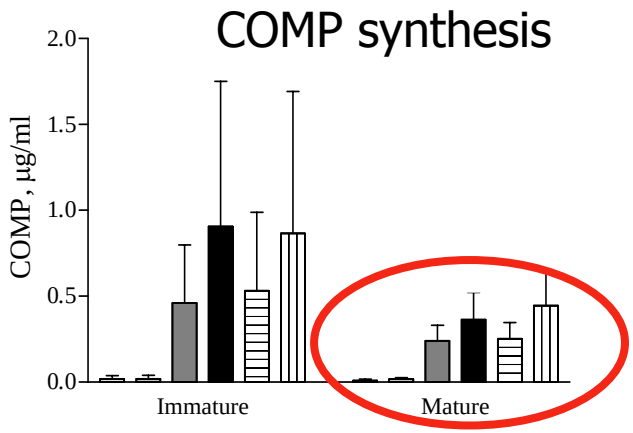
- What are the mechanisms of tendon aging?
  - Failure of adaptation/functional repair
  - Degeneration processes

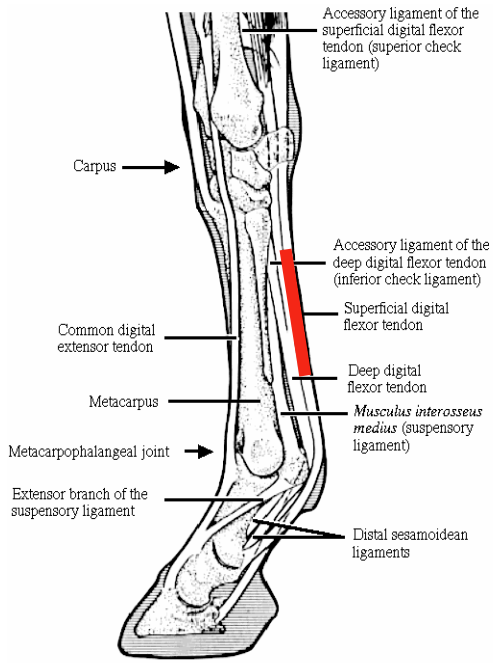
Failure of adaptation - 'Aged' tenocytes have reduced responsiveness







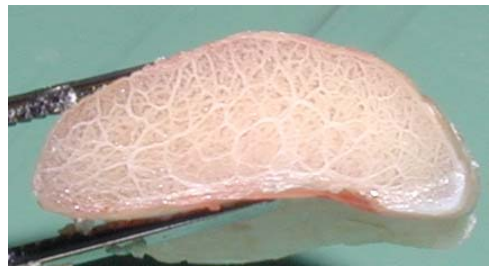


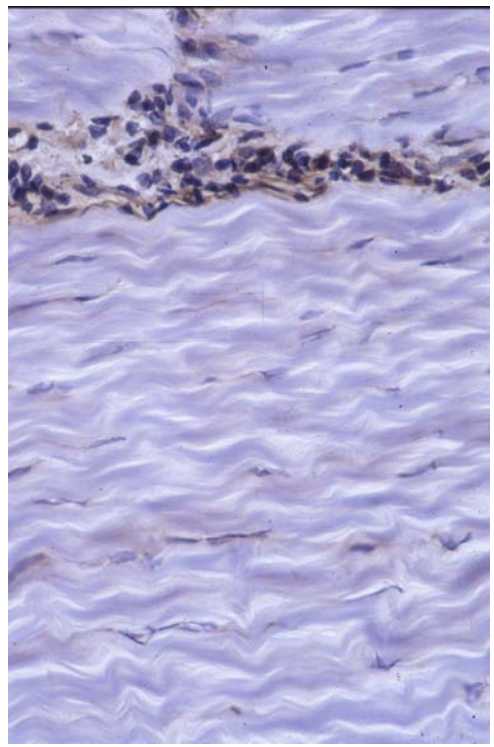


(Goodman et al. (2004) Biorheology, 41, 613-628)

Failure of adaptation - Reduced levels of anabolic growth factors (TGFβ) within the tendon after skeletal maturity

- TGFβ isoforms prominent in fascicles and endotenon septa during growth
- Decline in staining in fascicles after skeletal maturity

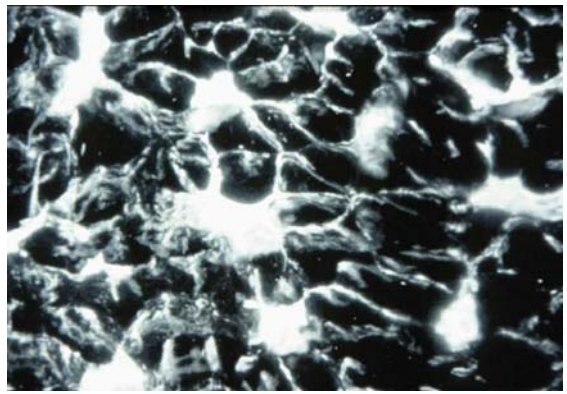




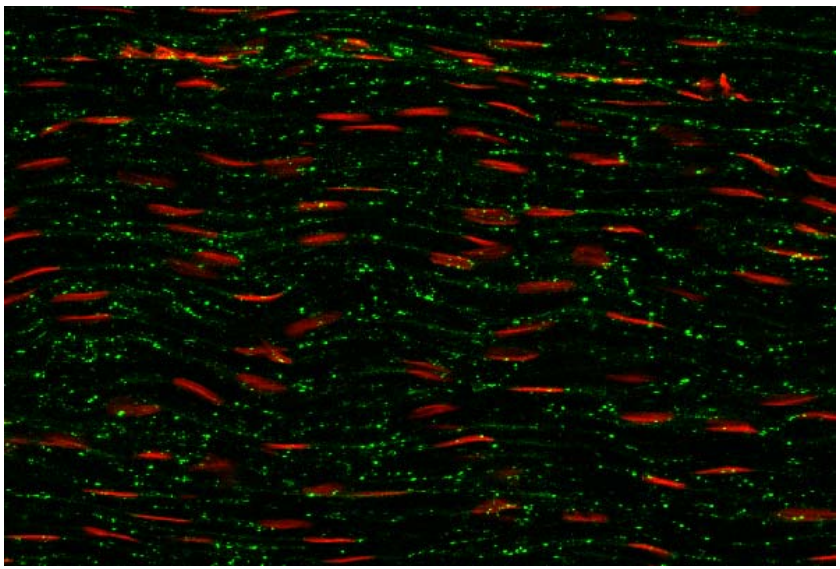
(Cauvin, Goodman, and Smith - unpublished)

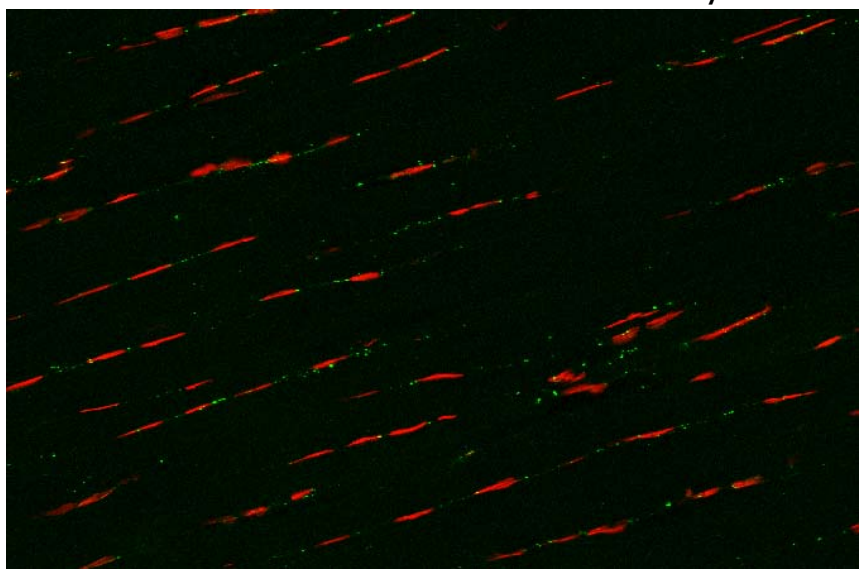
Failure of adaptation - reduced intercellular communication

- Reduced gap junction numbers with age
  - ?Reduced co-ordinated response to load after skeletal maturity



Courtesy of Dr Jim Ralphs, Cardiff University

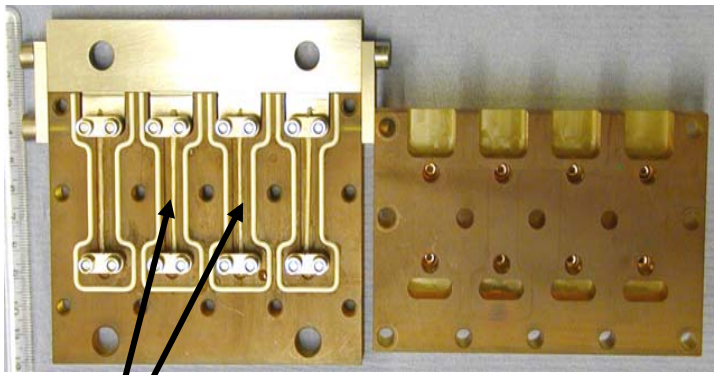




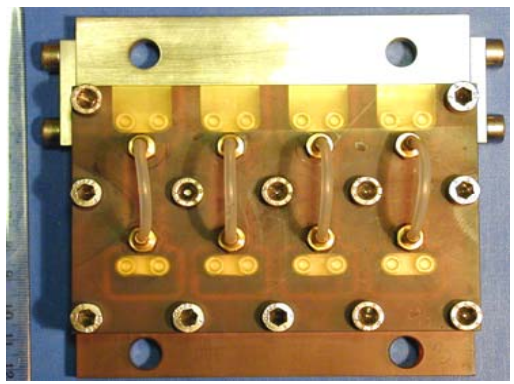
(Stanley, Patterson-Kane – unpublished)

Mechanisms of degeneration

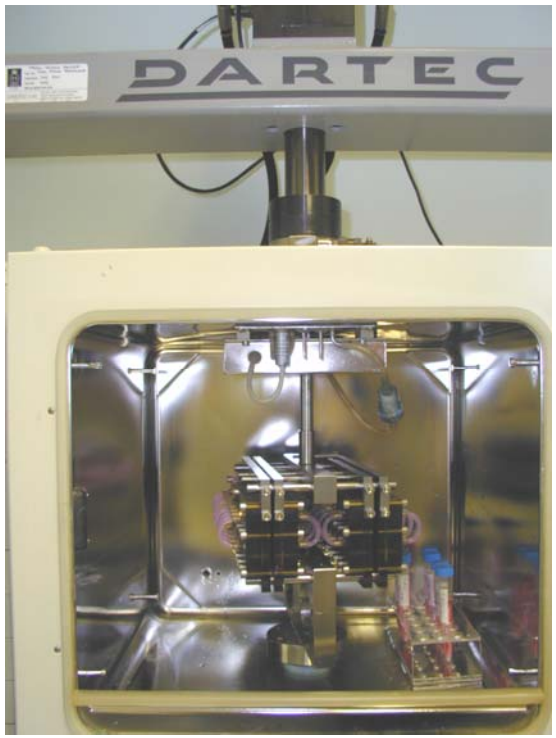
- Hypothesis – Ageing is a biologically active process in response to cyclical loading



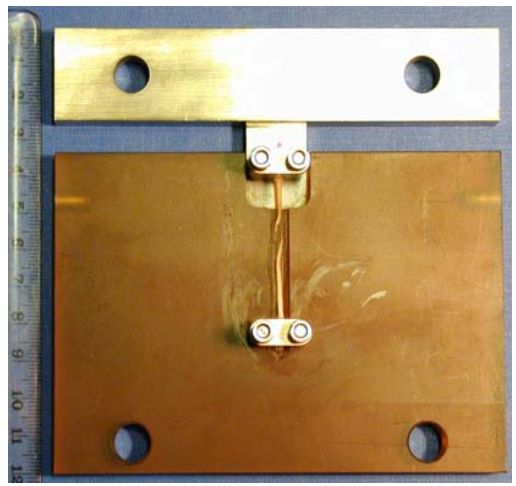
Cassette in open position to load explants



Cassette closed for strain application



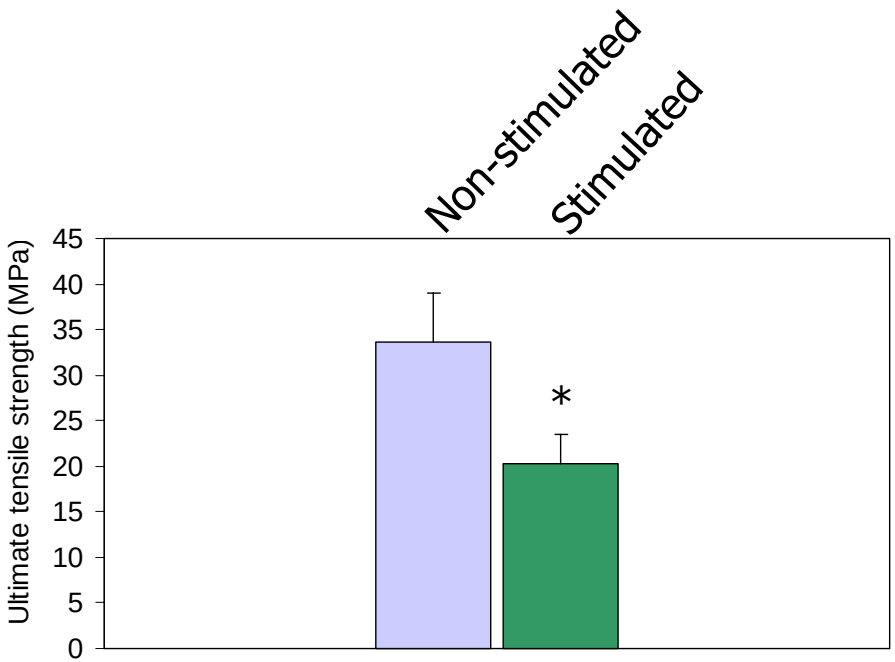
Cyclical loading under culture conditions



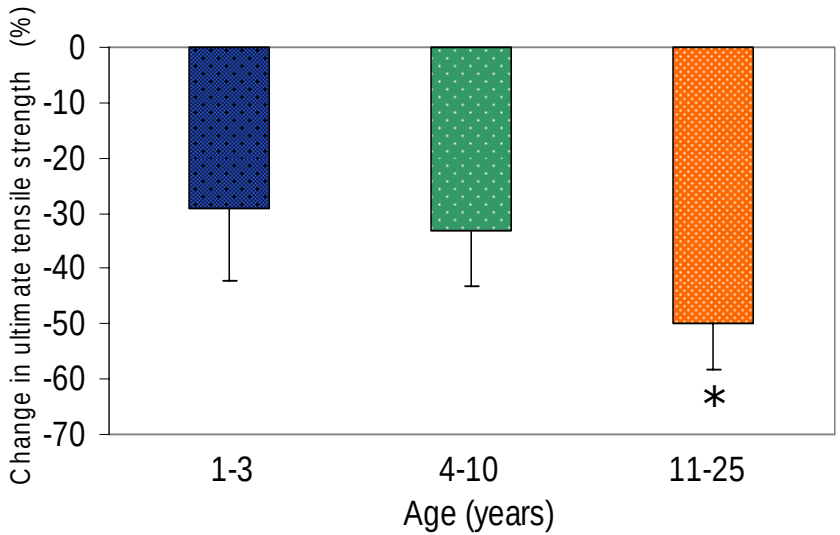
Cassette for tensile strength test shown post-test

Cyclic loading reduces tensile strength of explants

- Cyclical strain (1 Hz, 5%) for 24 h reduces the ultimate tensile stress (UTS) of explants
- The reduction is greater in aged samples

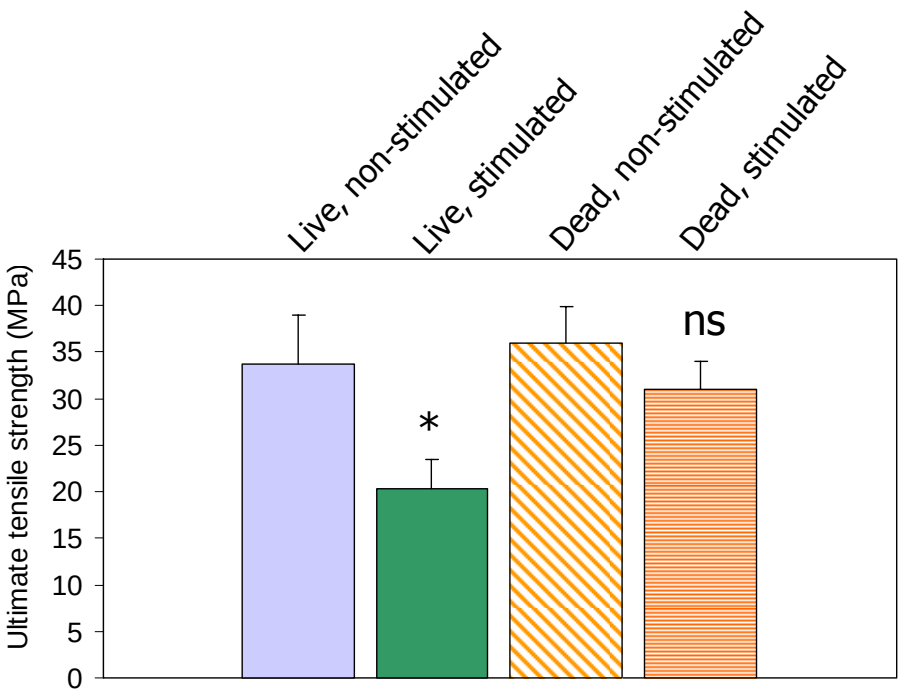


* p≤0.05, n=20

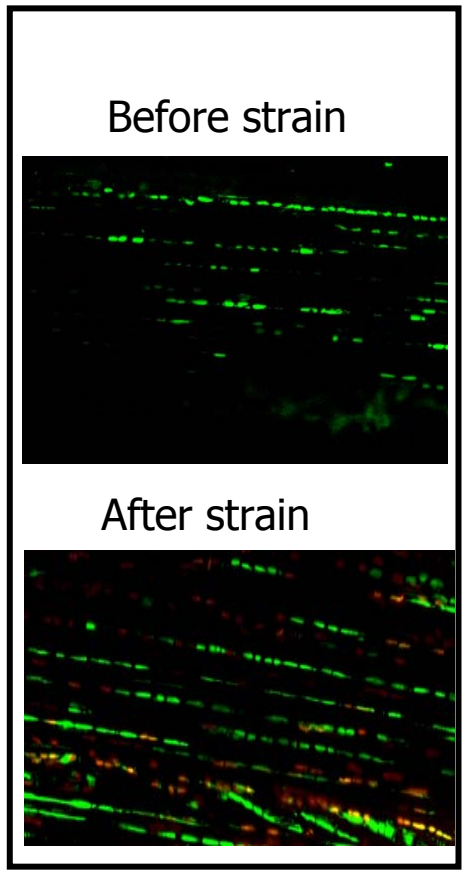


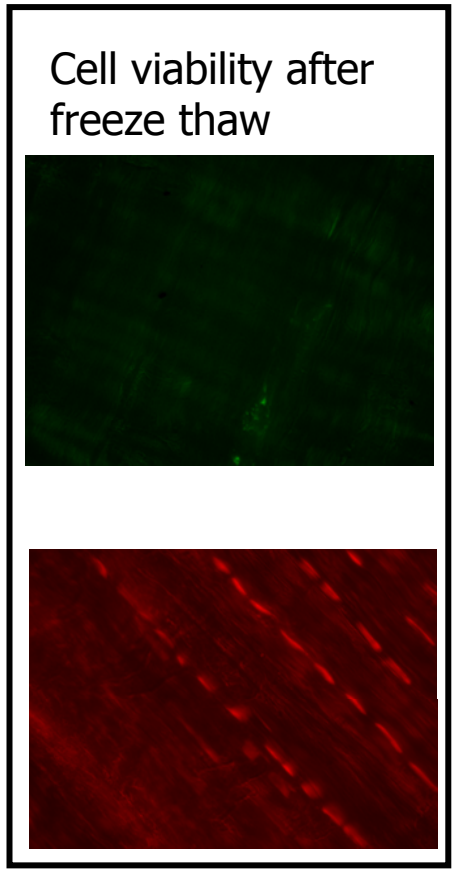
Loss in UTS induced by cyclical load requires viable cells

- Changes in UTS prevented by
  - Freeze-thawing
  - Sodium azide



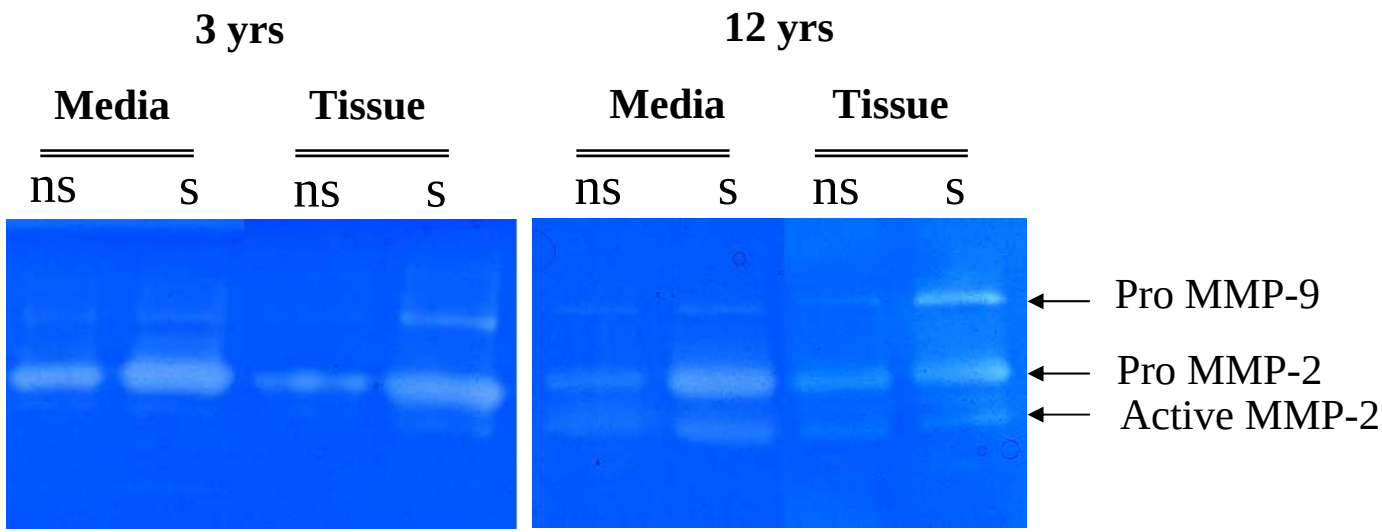
* p≤0.05, n=12 for dead expts





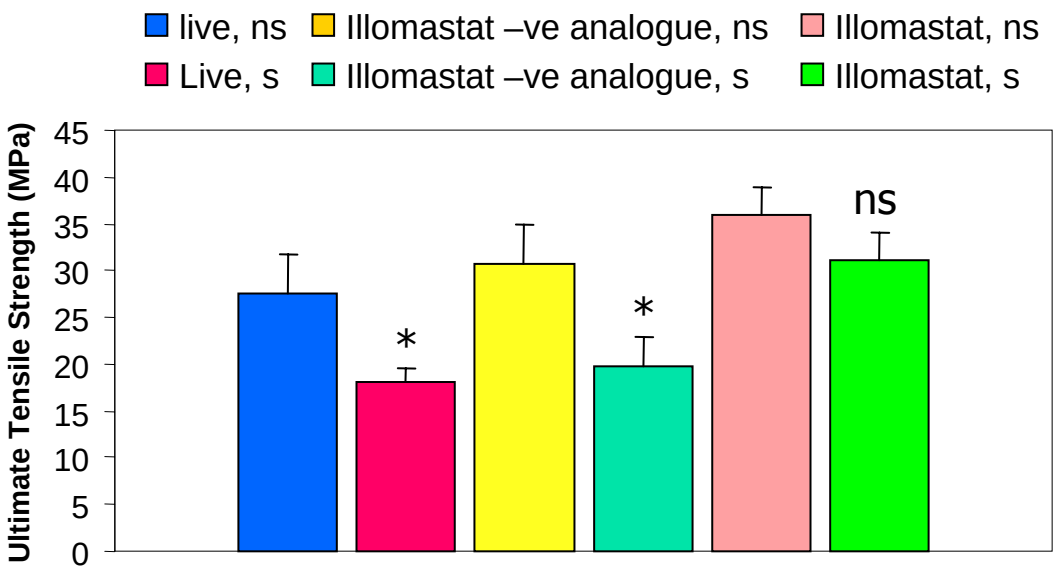
Cyclical loading induces MMP expression and activity

- Cyclical strain induced the expression of total MMP-2 by 2 to 5-fold, and active form by up to 3-fold
- Pro-MMP-2 induced to similar level at all ages, but active form induced more in the aged specimens



MMP activity is required for the loss in ultimate tensile strength induced by cyclical loading

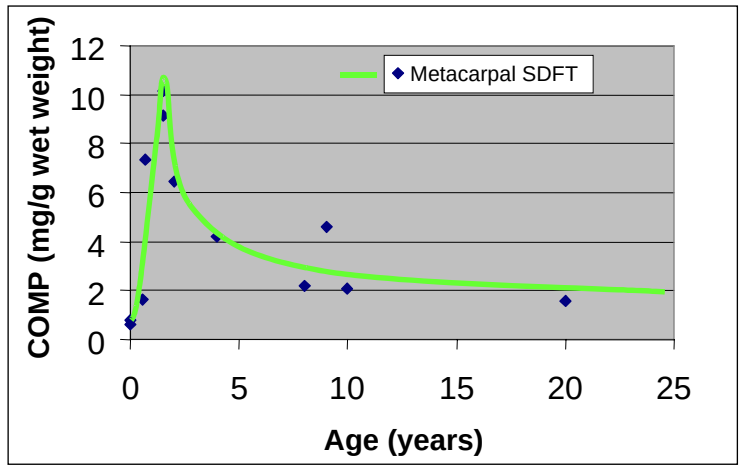
- The broad-spectrum MMP inhibitor (Ilomastat) reduced the magnitude of load-induced decrease in UTS
- The inactive analogue of Ilomastat failed to modify strain-induced decreases in UTS

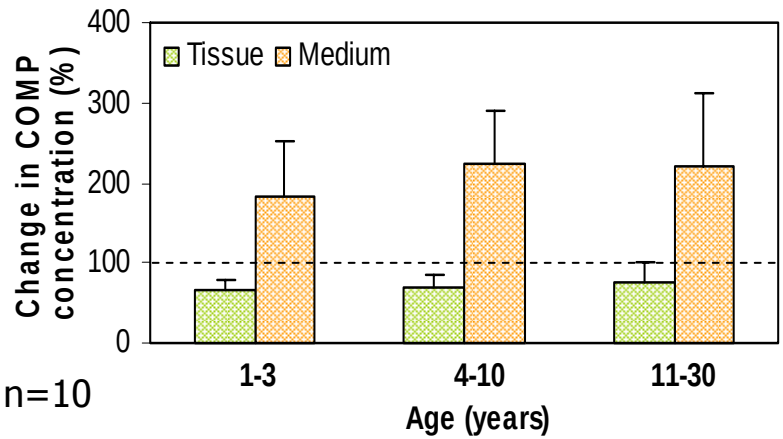


* p<0.05, n= 4

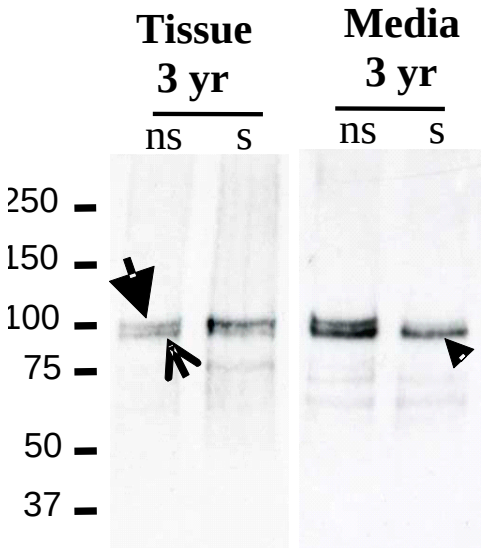
Cyclic loading also induces the loss of a labile integral matrix constituent

- COMP is a labile component of tendon
  - Decreased with aging and exercise
- Cyclical loading promotes the release of COMP from tendon
  - Fragmented
  - No effect of age

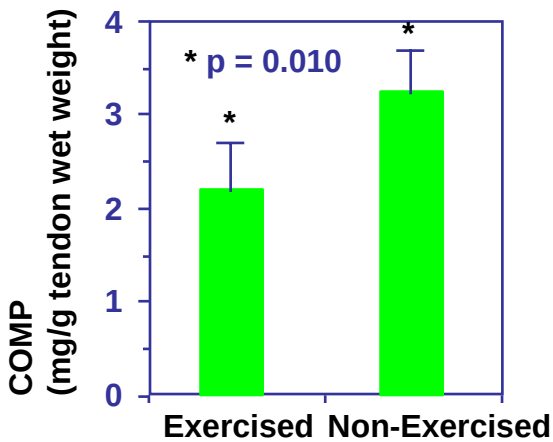




In vitro

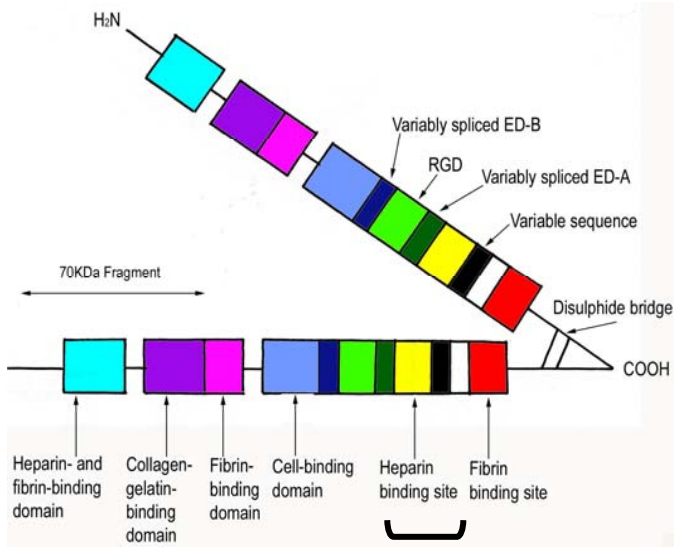


In vivo

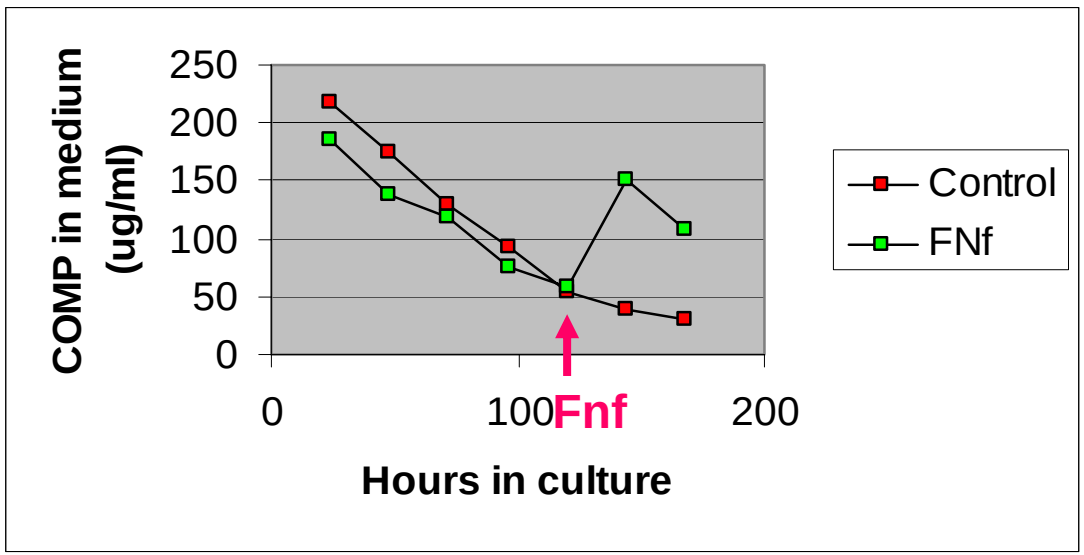


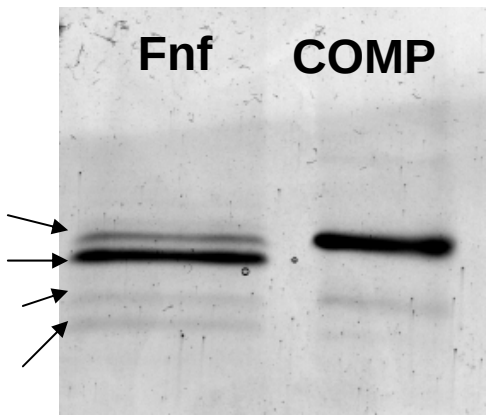
The action of matrix fragments ('matrikines') on tendon explants

- Matrix fragments induce a loss of COMP from tendon explants
  - 40kDa C-terminal fibronectin fragment (FNf-HepII)



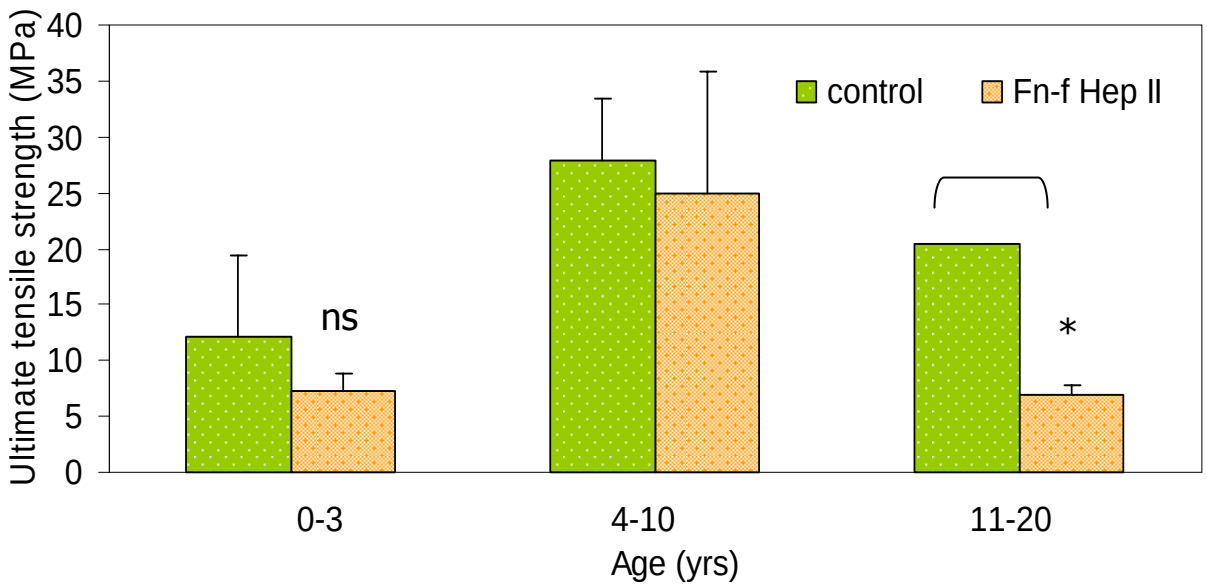
Fnf
HepII



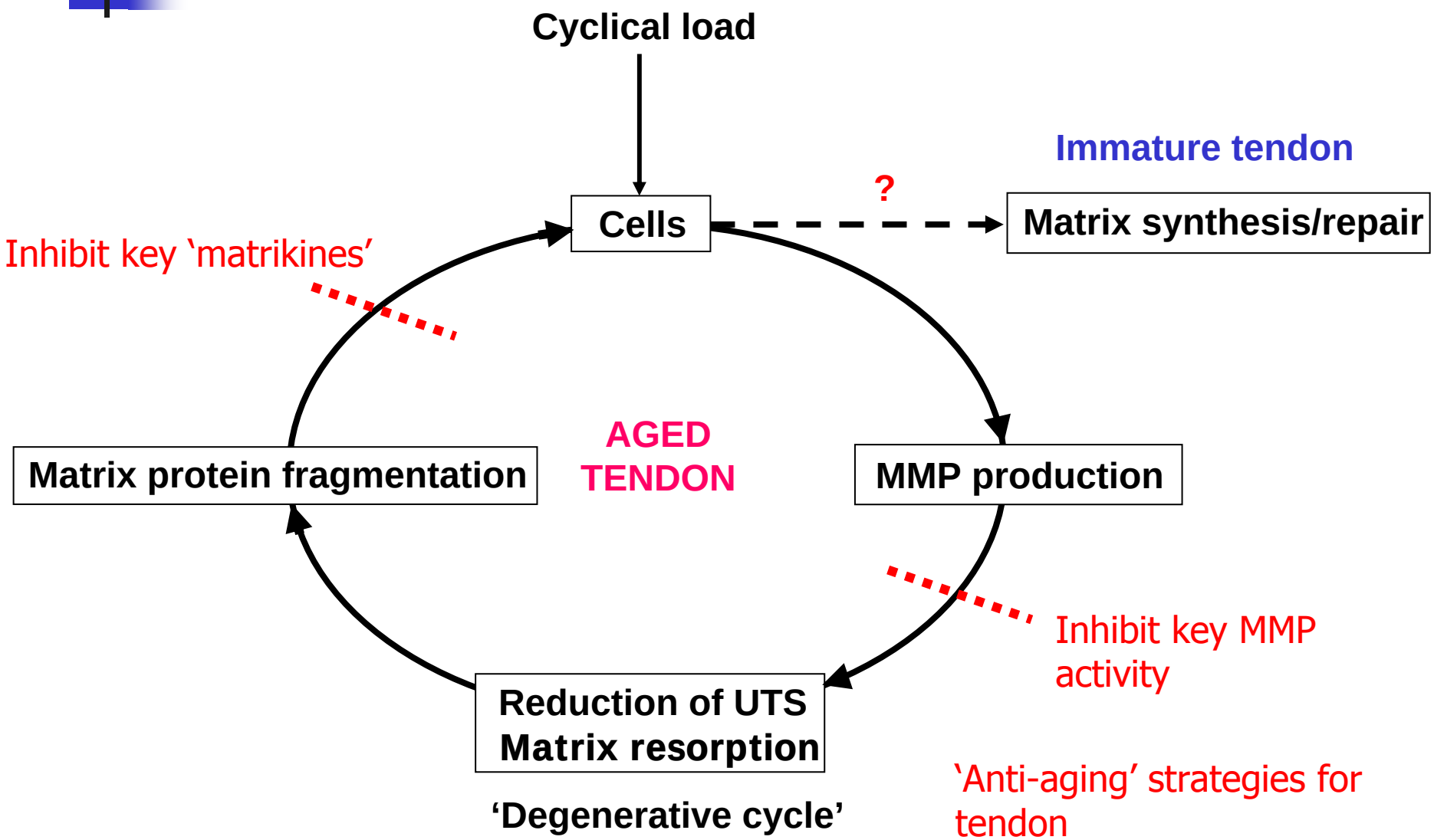


Matrix fragments induce a loss of UTS in aged tendon explants

- BUT Fn-f Hep II did not induce loss of tensile strength of younger tissues
- Similar to the effects of applying strain
  - Mechanism? - FNf induces MMPs (Homandberg et al., 1996)



Conclusions – proposed mechanism for soft tissue aging



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- A. Goodship, RVC and UCL – loading apparatus

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