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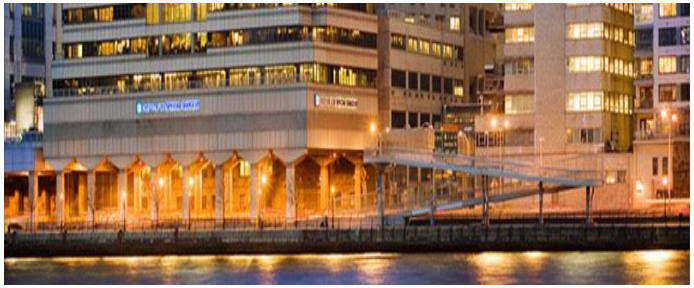
Mechanisms of Cartilage Damage

Mary B. Goldring, PhD



Senior Scientist, Hospital for Special Surgery, New York, NY
Co-Director, Tissue Engineering, Regeneration & Repair Program
Professor of Cell & Developmental Biology
Weill Cornell Medical College & Weill Cornell Graduate Program of Medical Sciences

Major Points

- Complexity of normal cartilage matrix and **inadequate repair mechanisms** makes it difficult to reverse cartilage damage once OA progresses
- Matrix metalloproteinase, MMP-13 has a pivotal role in OA progression as the **collagenase** that preferentially degrades type II collagen, but its inhibition does not block all aspects of pathogenesis.
- Similar signaling pathways and downstream transcriptional regulators are induced by **inflammatory, mechanical, and oxidative stresses**.
- The heterogeneity of **OA phenotypes**, represented in different in vitro and in vivo models, demonstrate common mechanisms over the time course of initiation and progression but present challenges for therapeutic development.

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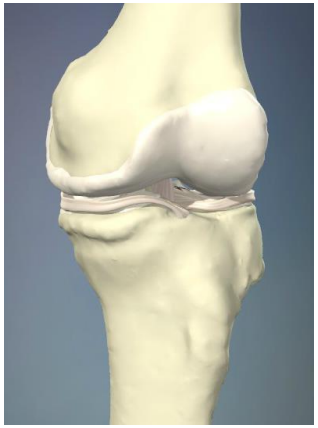
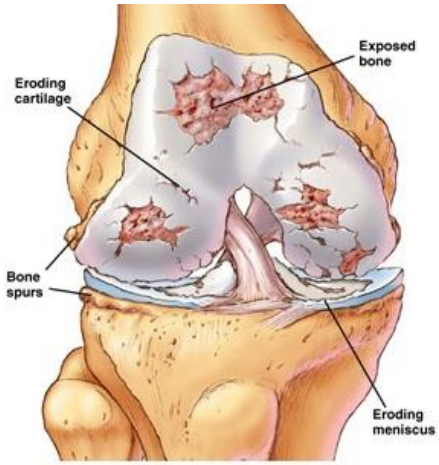
OA is a “joint” disorder



- OA is characterized by alterations in the composition, structural organization and functional properties of all of the joint tissues:
  - Cartilage
  - Calcified cartilage
  - Bone
  - Synovium
  - Ligaments, menisci, tendons

Domino affect



- The alterations are mediated via *mechanical damage (disruption)* and *cellular mechanisms* that modify the composition, structure and properties of the tissues.
- Alterations in a single tissue eventually will adversely affect all of the joint tissues

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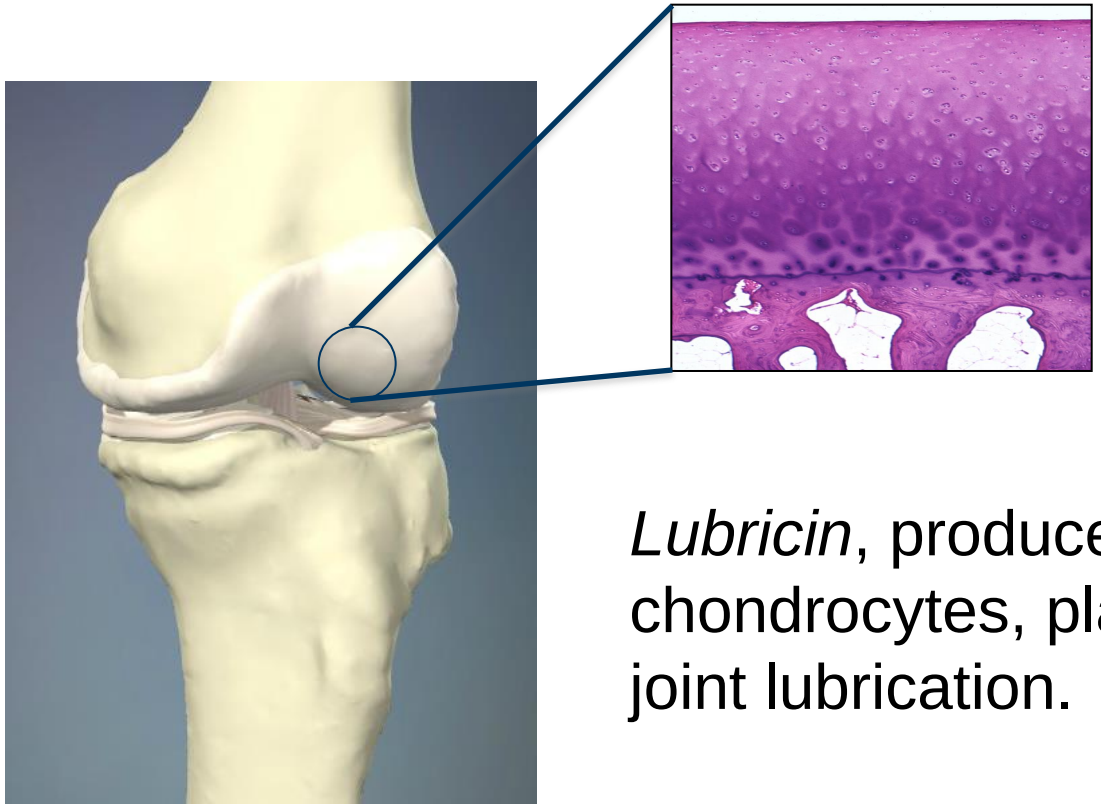
Mechanism of joint “lubrication”: Role of *lubricin*

- Cartilage is surface is uniquely adapted to transfer of loads (exhibits a unique low friction property orders of magnitude less than ice)



Lubricin, produced by superficial chondrocytes, plays a key role in joint lubrication.

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Lubricin

- *Lubricin* is a product of the *PRG4 gene* that is produced by superficial articular chondrocytes and synovial lining cells

- Loss of function mutations in *PRG4* causes camptodactyly-arthropathy coxa vera-pericarditis syndrome, which is associated with early OA
  - *Marcelino et al. Nat Genet 1999; 23:319-22*

- Genetic knockout of *Prg4* in mice results in OA pathology
  - *Rhee et al. J Clin Invest 2005; 115:622-31*

- *Lubricin* provides synovial fluid its capacity to dissipate energy under load; and is chondroprotective in *Prg4* knockout mice and in a rat OA model
  - *Gleghorn, Bonassar et al. J Orthop Res 2009; 27:771-7*
  - *Flannery, Bonassar et al. Arthritis Rheum 2009; 60:840-47*

- Forced *PRG4* expression protects against the development of OA
  - *Ruan, Lee et al. Sci Transl Med. 2013 Mar 13;5(176):176ra34*

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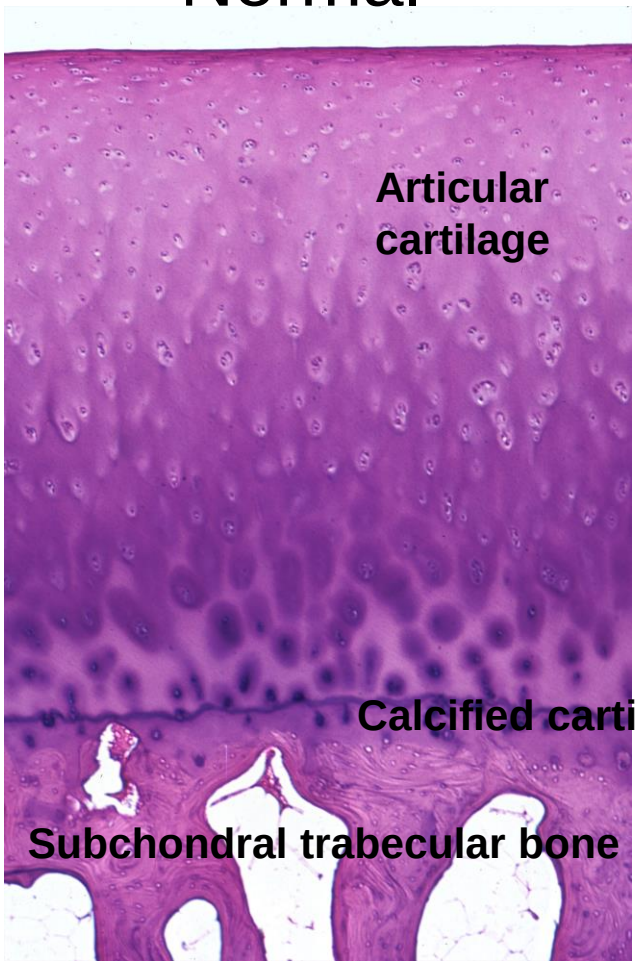
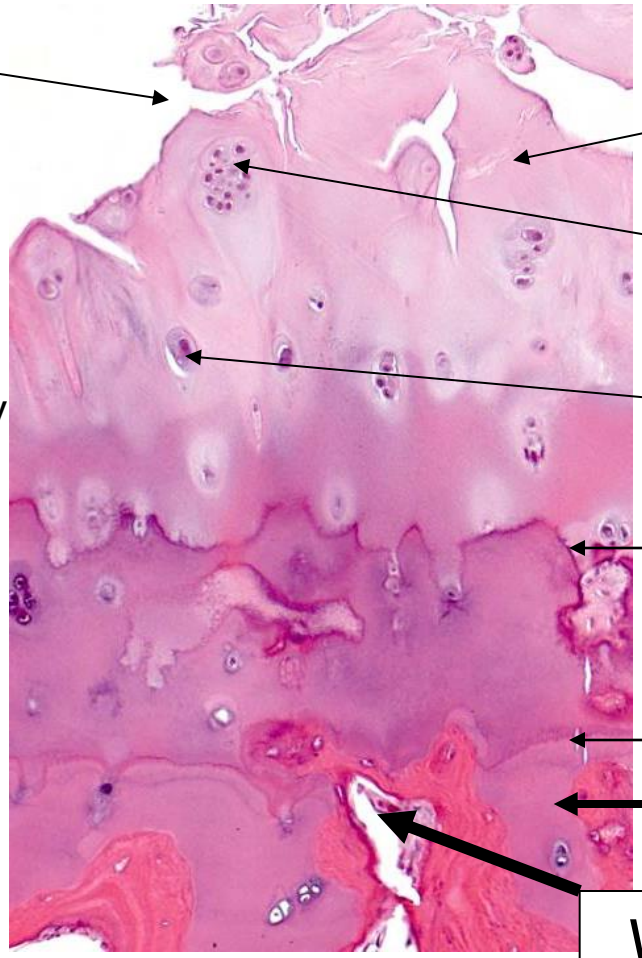
Cartilage Pathology: from homeostasis to OA

Normal



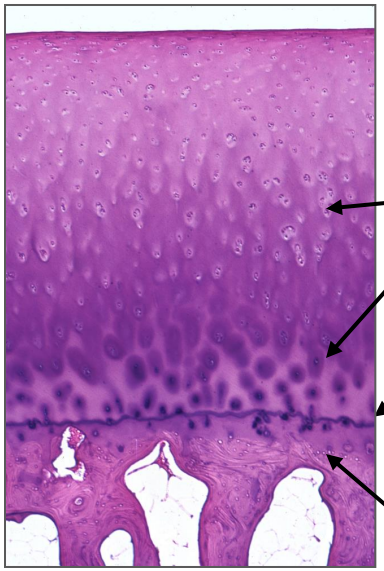
Mechanical
Inflammatory
Oxidative
Stresses

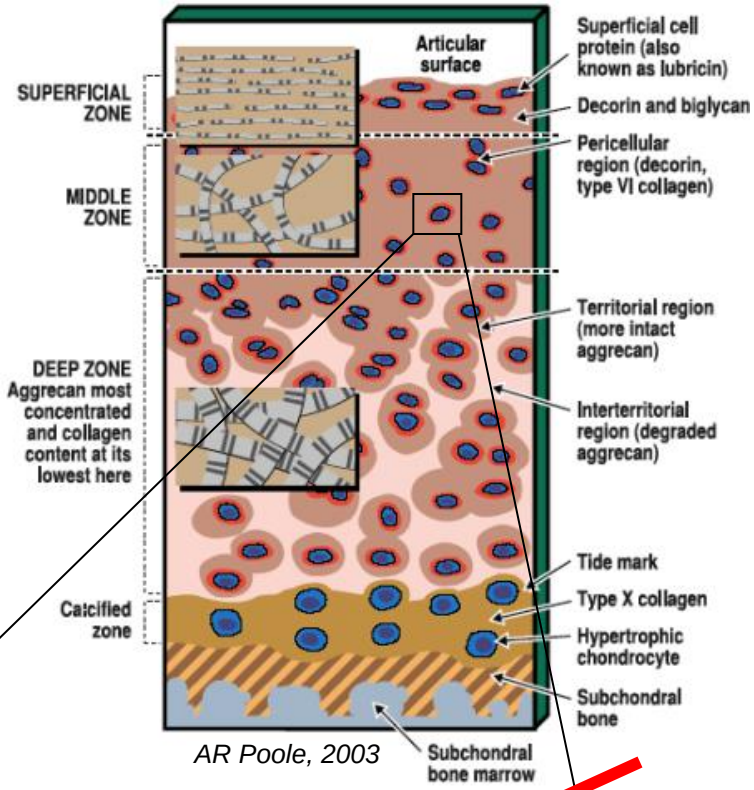
Osteoarthritis



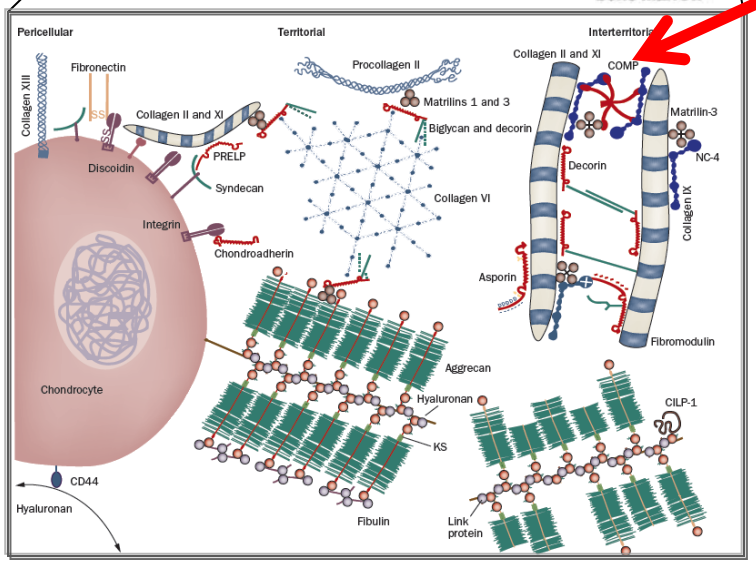
Loeser et al. Arthritis Rheum 2012; 64: 1697-1707

Normal articular cartilage



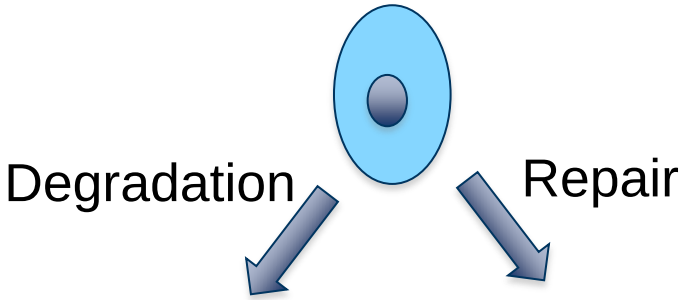


AR Poole, 2003



Heinegard & Saxne: Nature Rev Rheumatol 7:50-56, 2011

Chondrocyte



Low turnover
maintenance of
cartilage Matrix

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Evidence of adaptive capacity of articular cartilage

Effect of loading on cartilage deformation behavior and metabolism

- Methods: evaluated the effect of running (30 min) and drop landing on knee cartilage deformation using MRI and serum COMP levels
- Results: Serum COMP levels increased immediately after running and drop landing. Cartilage deformation was more pronounced after running than drop landing
- Conclusion: *In vivo exercise modulates cartilage morphology and the metabolic activity of chondrocytes*

www.photo-dictionary.com

Niehoff A et al. Osteoarthritis Cartilage 2011; 19:1003-10

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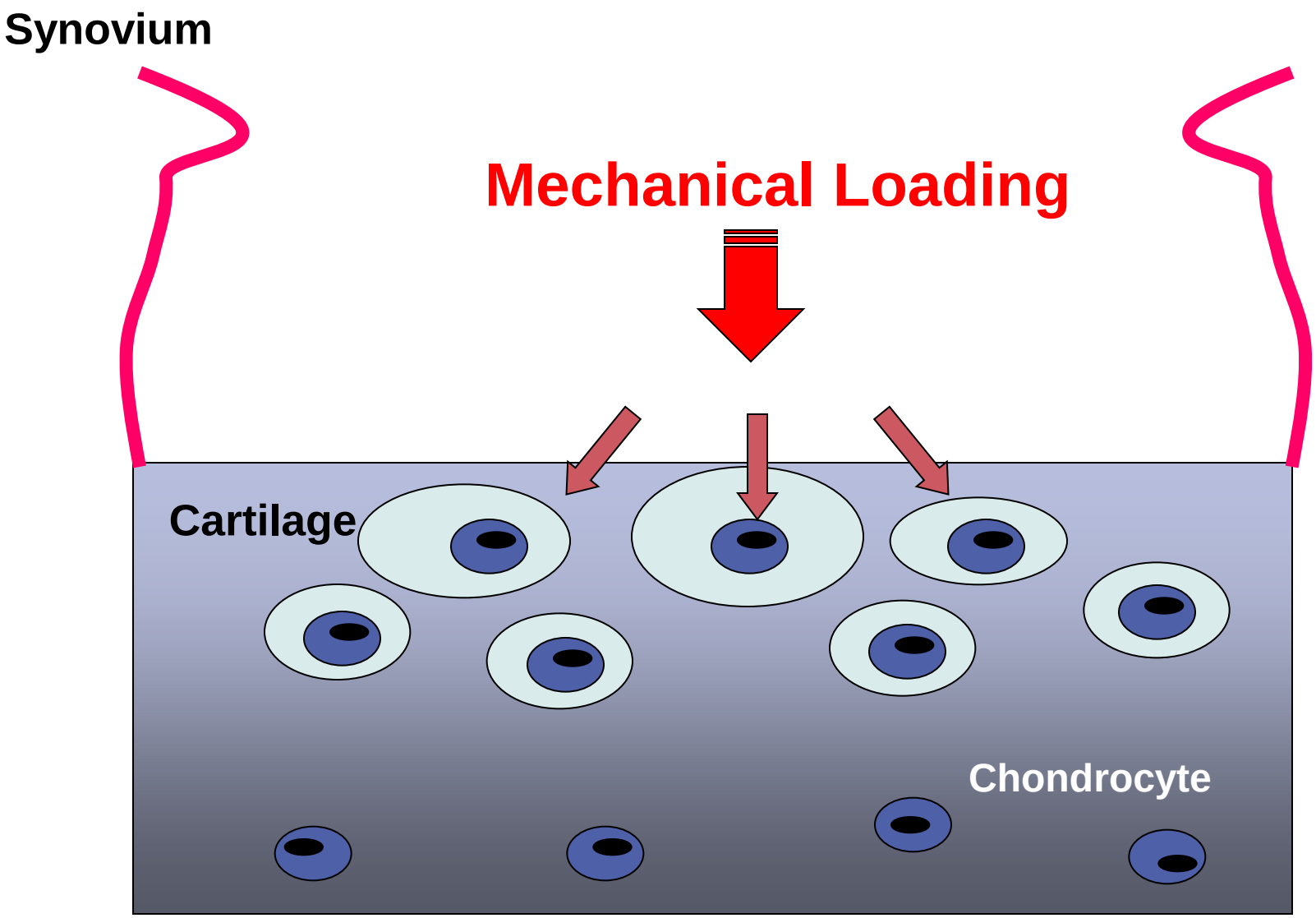
Adaptation of chondrocytes to mechanical stimulation



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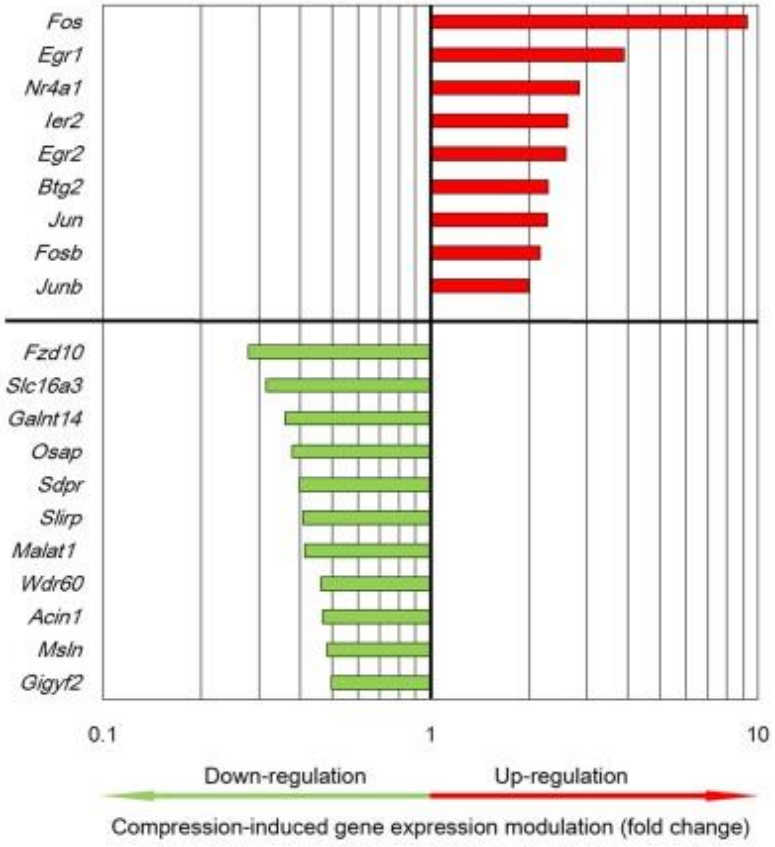
How does the chondrocyte *sense* its mechanical environment?

Chondrocyte mechano-sensors

- Ion channels (Trpv4)
- Integrin-mediated
- Cytoskeletal deformation
- Fluid flow

Guilak F. Best Pract Res Clin Rheumatol. 2012; 25:815-23

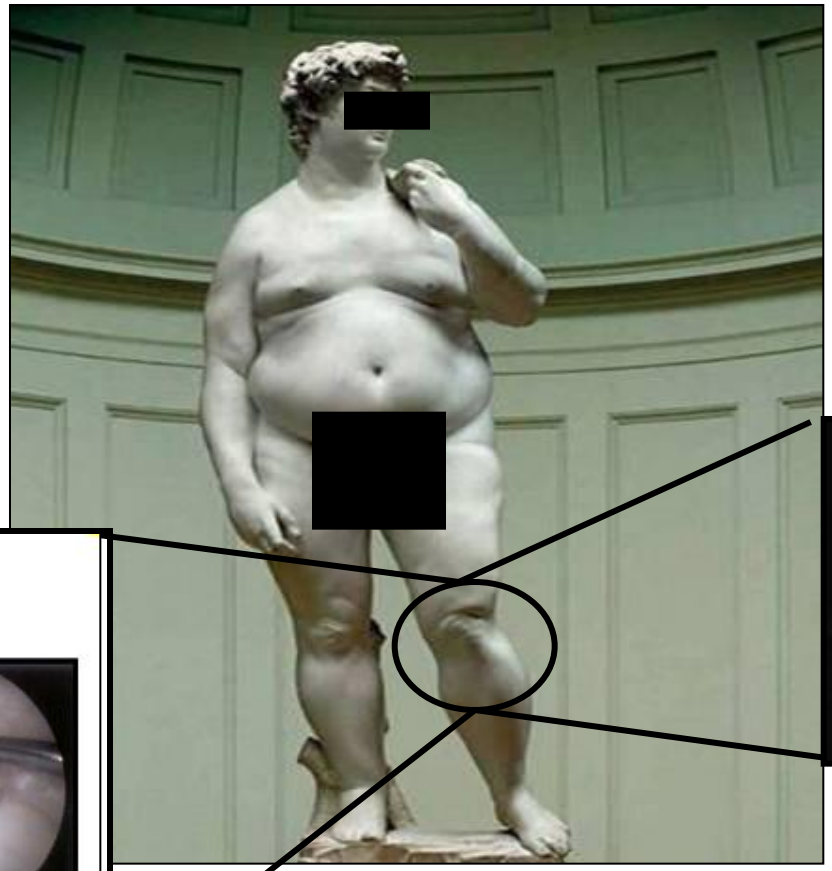
Compression-induced genes



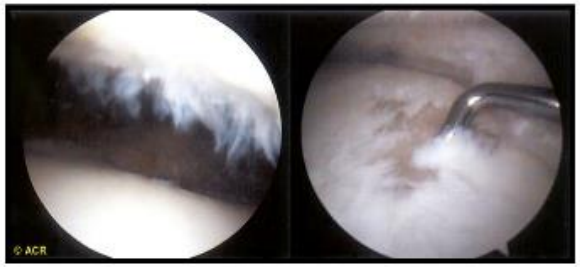
Bougault c et al. PloS One. 2012; 7(5)e36964

Michelangelo's David: the late years

<u>OA Risk factors:</u>
-Injury
-Age
-Genetics
-Inflammation
-Obesity/metabolic syndrome



Osteoarthritis: knee (arthroscopy)



<u>Questions:</u>
What has happened?
Why did this happen?
Could it have been prevented or treated?

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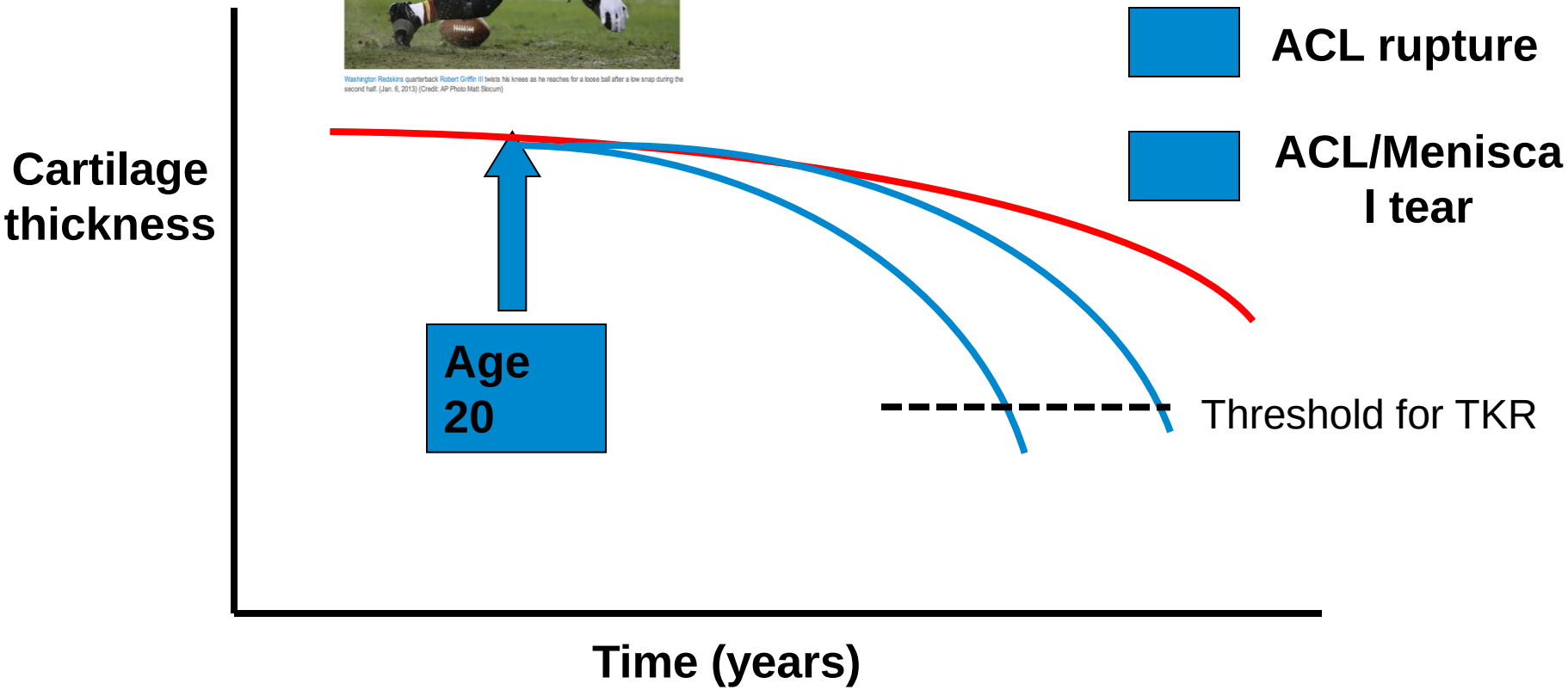
Effect of extent of joint injury on natural history of OA

Washington Redskins quarterback Robert Griffin III twists his knees as he reaches for a loose ball after a low snap during the second half. (Jan. 6, 2013) (Credit: AP Photo Matt Slocum)



Murrell et al. Am J Sports Med. 2001; 29:9-14
Maffulli et al. J Arthroscopic Rel Res. 2003; 19:685-90
Lohmander et al. Am J Sports Med 2007; 35:1356-79

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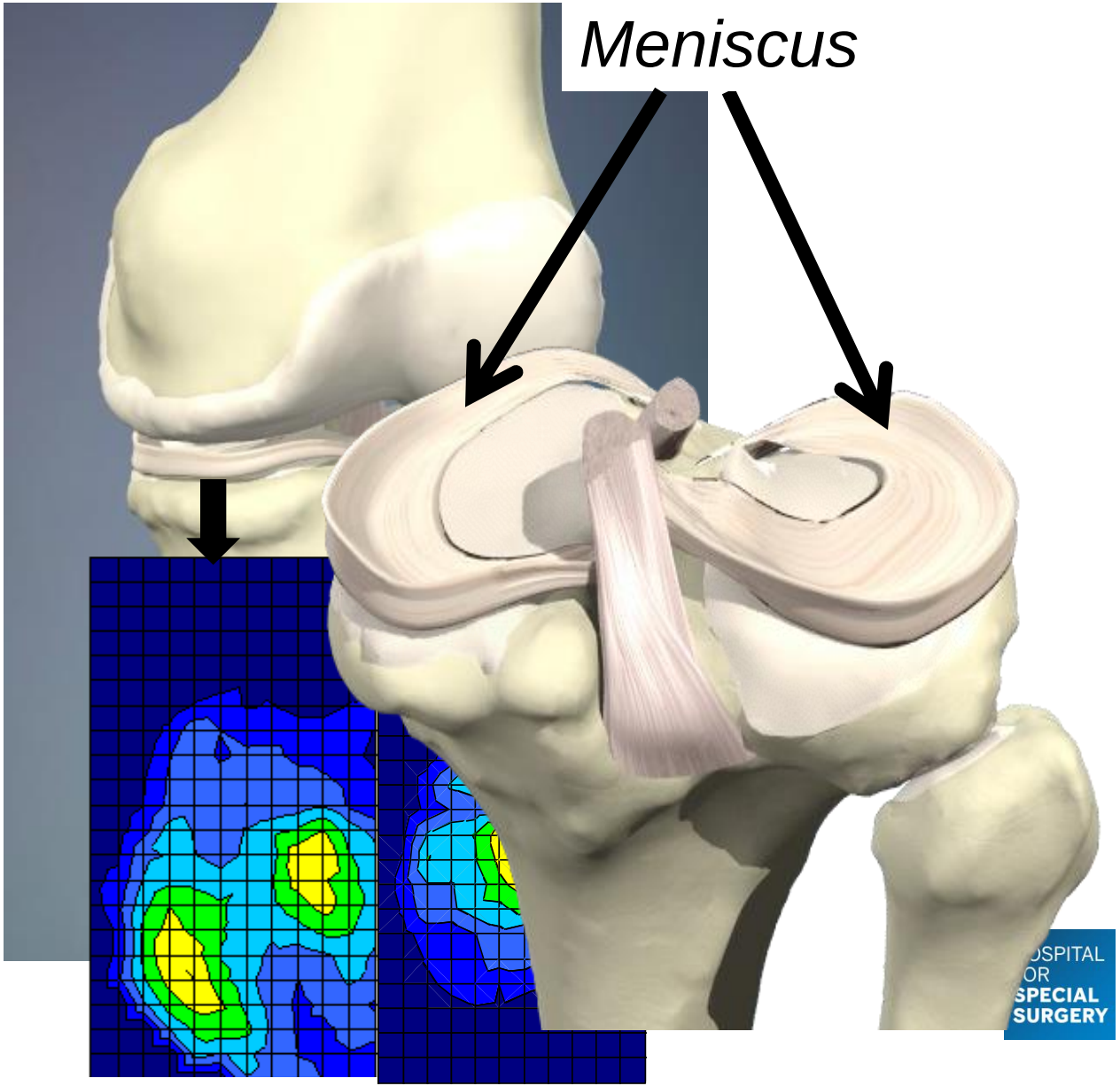
Distribution of contact forces in the knee

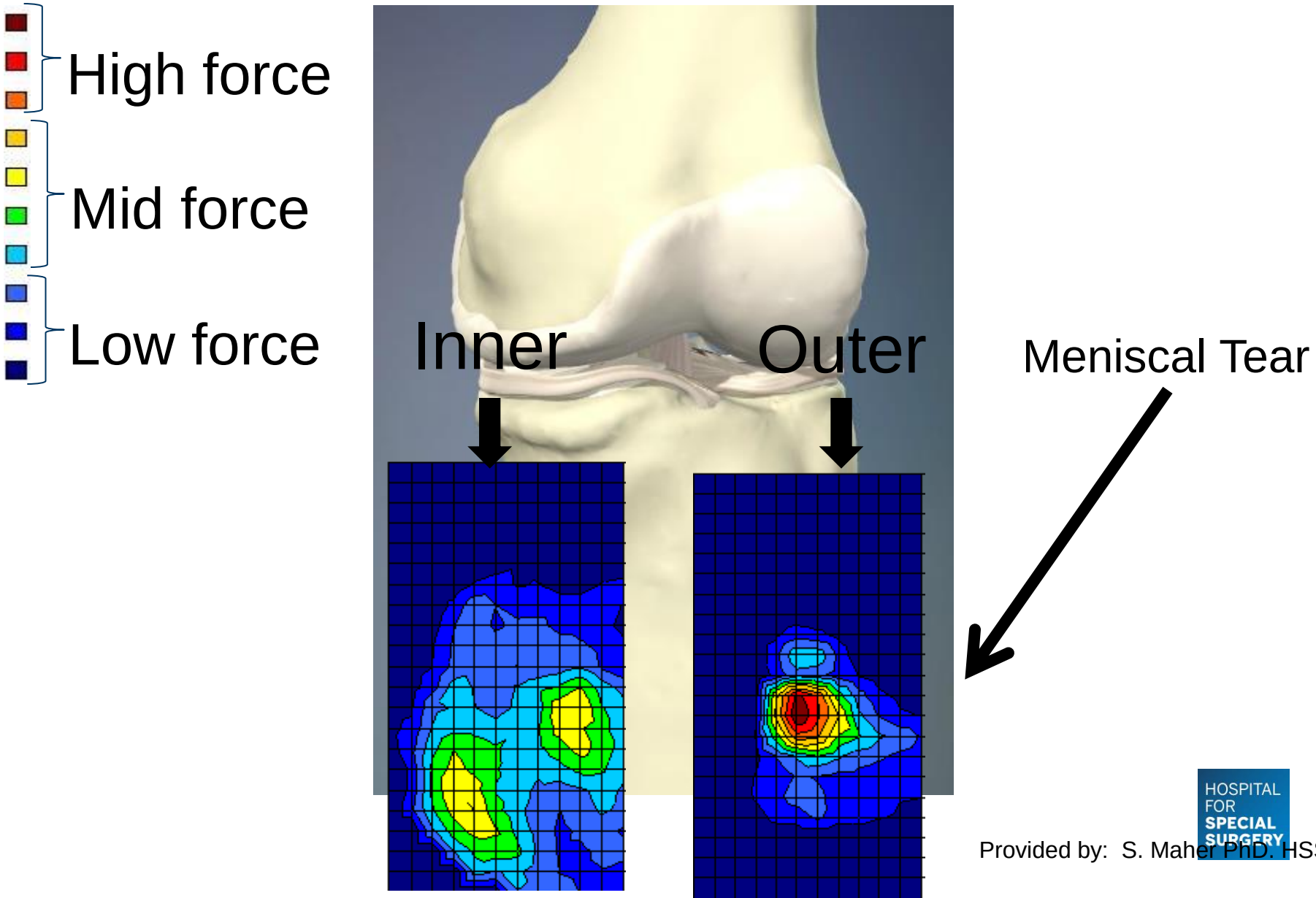
High force

Middle force

Low force

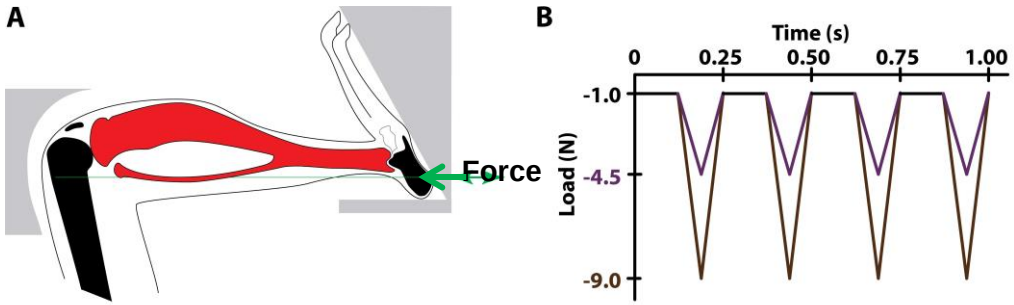


Provided by: S. Maher PhD. HSS



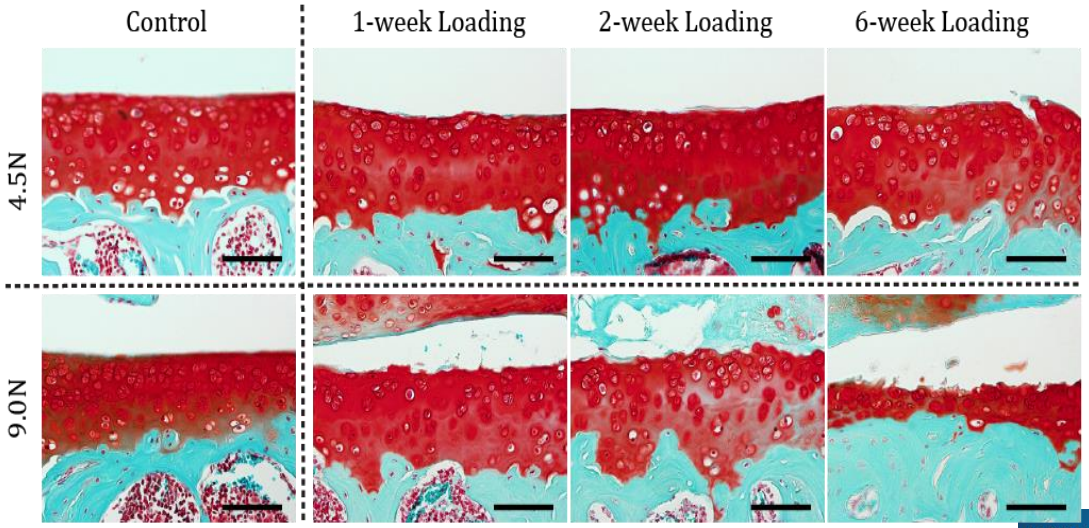
Provided by: S. Maher PhD. HSS

Non-invasive tibial loading model: Cartilage and bone changes are dependent on the magnitude of load



A) Schematic of in vivo mouse tibial loading, and (B) loading waveforms with peak compressive loads of 4.5N and 9.0N

- Cartilage loss
- Subchondral cortical thickening
- Changes are topographically associated



Ko, Goldring, van der Meulen et al. Arthritis Rheum 2013; 65:1567-78
Ko et al., J Orthop Res. 2016 (single loading regimen)

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Age-associated changes in chondrocytes

- Altered pattern of matrix synthesis
- Increased production of matrix degrading enzymes
- Increased apoptosis
- Decreased capacity to handle stress
  - Changes in sensitivity to growth factors
  - Altered proliferative capacity

Age-related alterations in the composition and properties of cartilage increase its susceptibility to mechanical damage.

Loeser et al. Arthritis Rheum. 2012; 64:1697-1707

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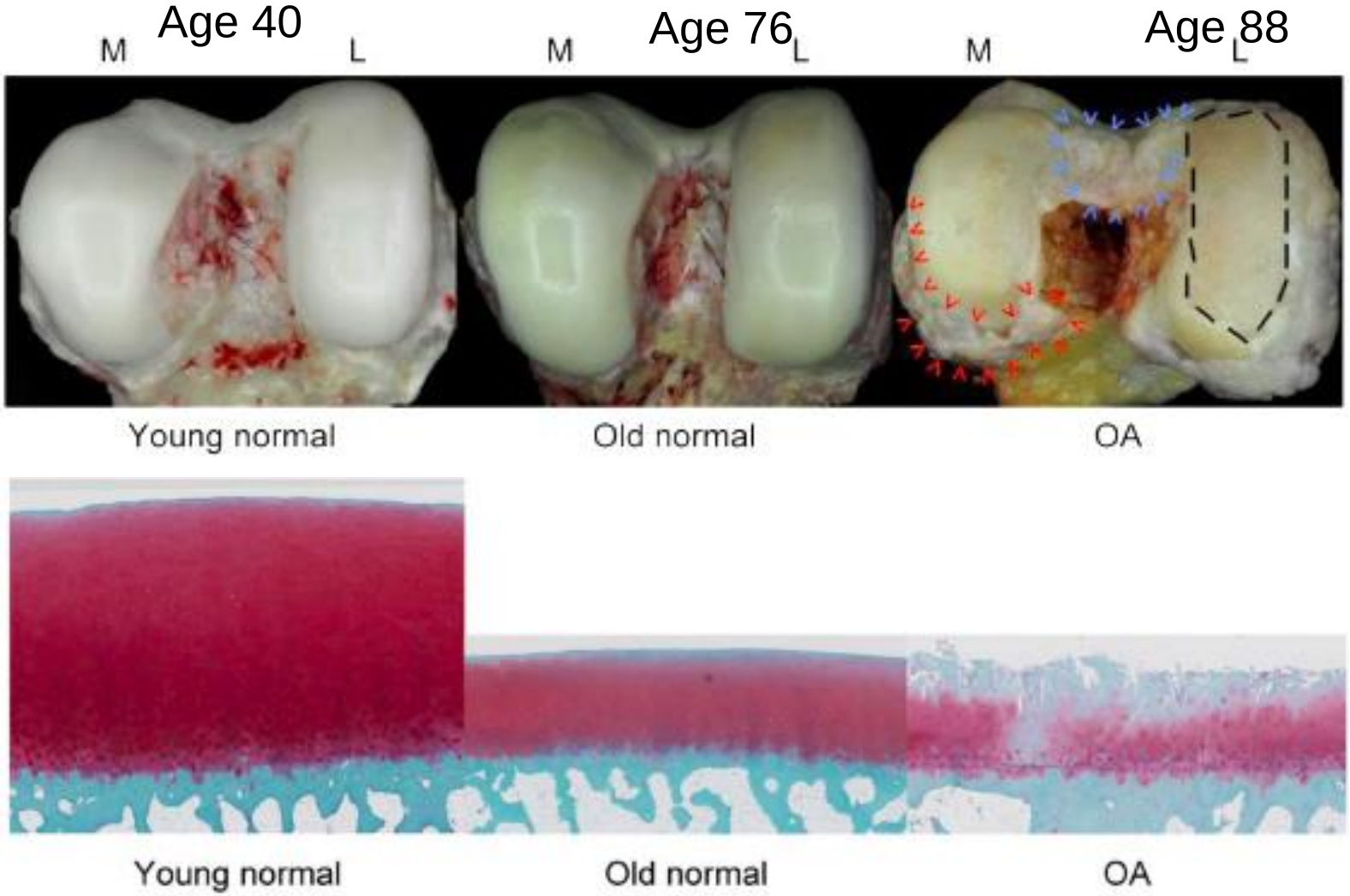
Effects of aging on articular cartilage



Age-related changes increase susceptibility to mechanical damage

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Lotz M & Loeser RF: Bone 2012

OA is associated with a chondrocyte "*catabolic state*"

- **Decreased aggrecan content**
  - -decreased synthesis
  - -increased breakdown
- **Alterations in patterns of collagens synthesized**
  - -Switch from type II collagen to types I and X
- **Production of matrix degradation products**
  - -DAMPs, alarmins
- **Decreased expression of anabolic growth factors**
  - -IGF-1, TGF-β, etc.
- **Up-regulation of proteases**
  - -MMPs, aggrecanases, cathepsins
- **Production of proinflammatory mediators/cytokines**
  - -IL-1, IL-6, IL-8, MCP-1, VEGF, reactive oxygen species, nitric oxide, prostaglandins

Heinegard. Int J Exp Path 2009; 90:575-86
Maldonado and Nam. Biomed Res Int 2013:28483

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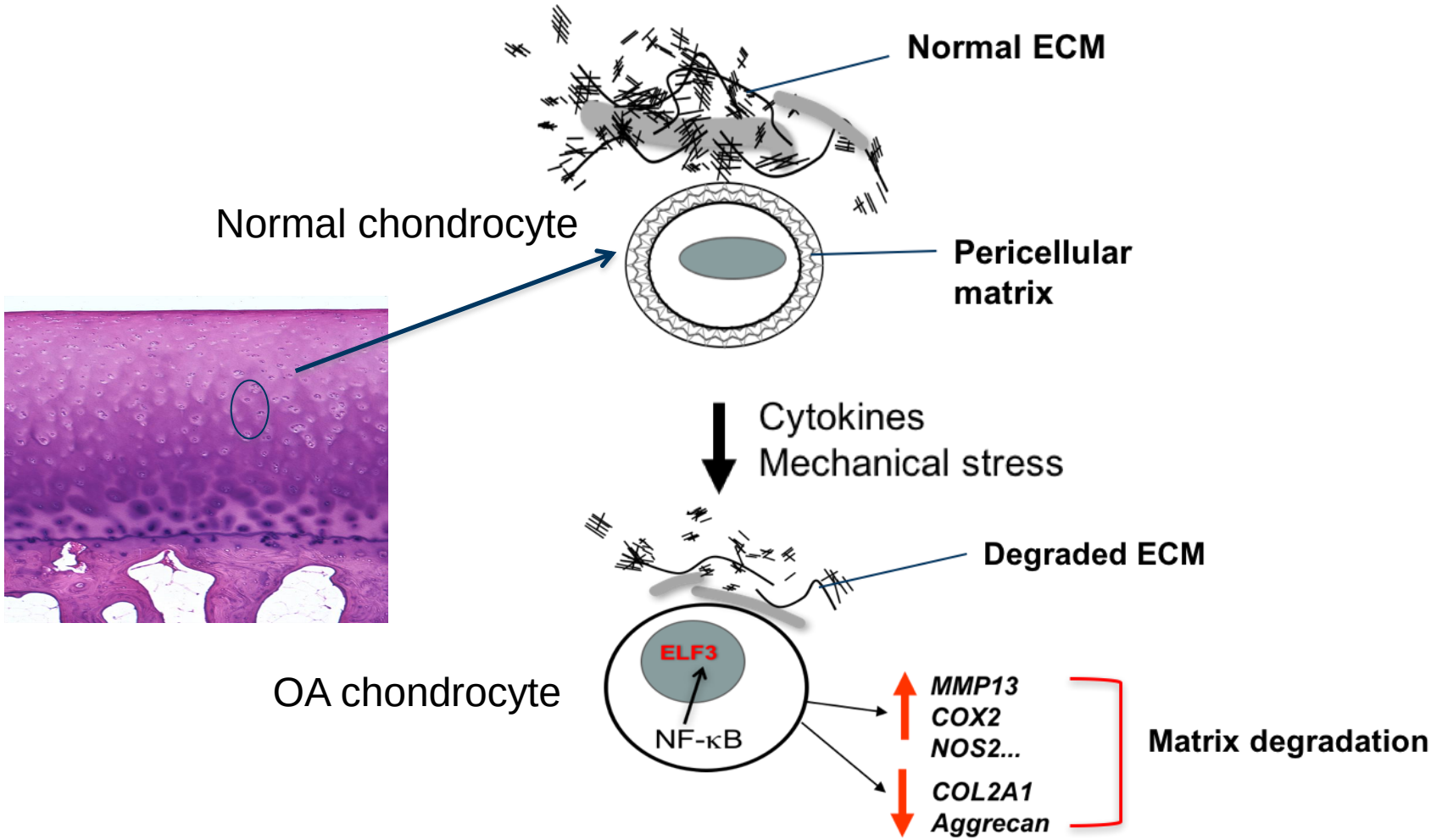
From homeostasis to osteoarthritis



ECM = Extracellular matrix

(Adapted from Marcu & Goldring et al., 2010)

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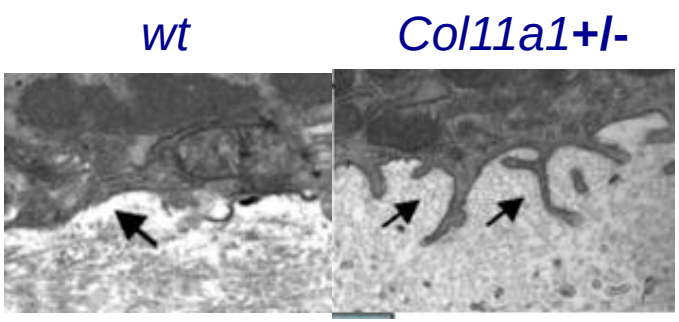
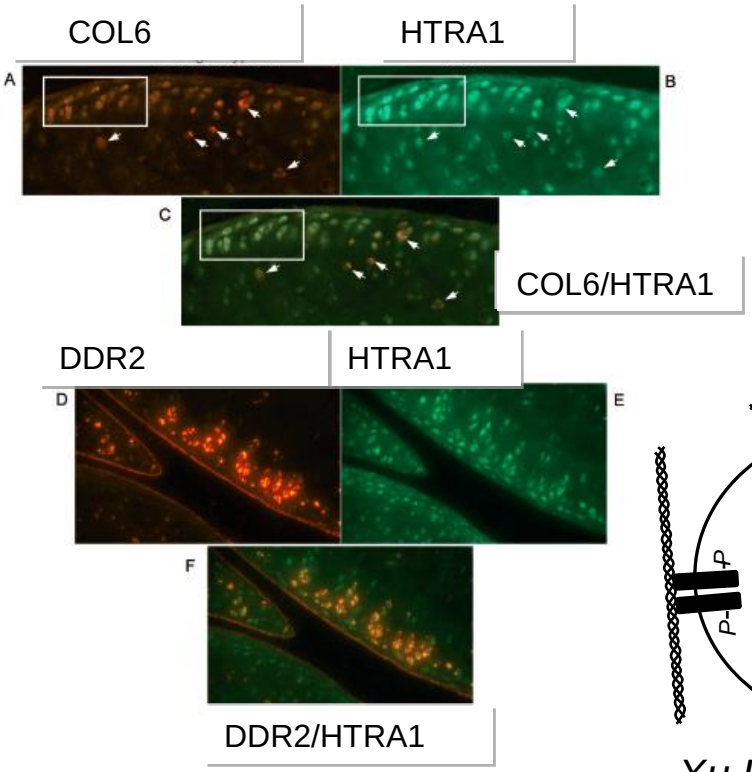
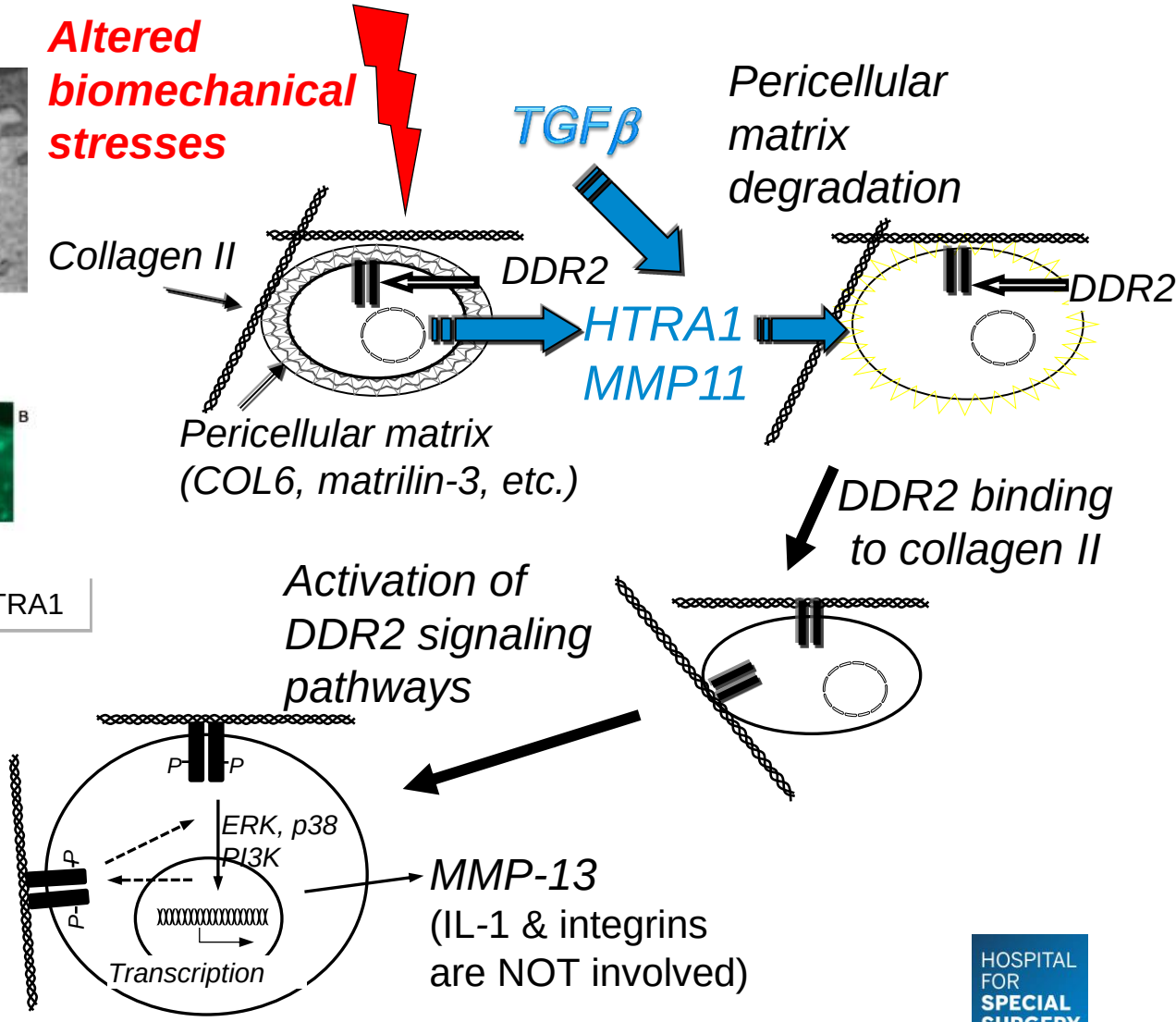
Role of pericellular matrix & discoidin domain receptor (DDR) 2







Xu L (Yefu Li) et al. Am J Pathol 2011;179:1338-1346

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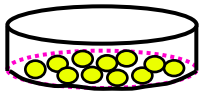
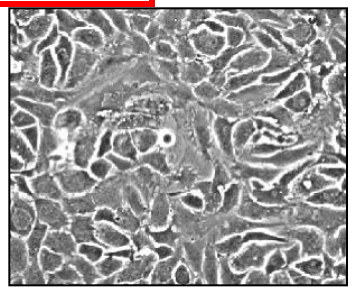
Role of matrix metalloproteinase-13 (MMP-13) in OA

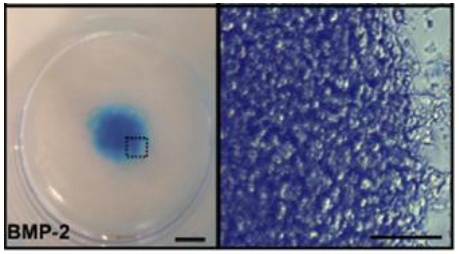
Mechanical stimulation
Inflammatory cytokines
Matrix degradation products

Monolayer





3D micromass



- Preferentially degrades type II collagen, the major collagen in cartilage matrix
- Marker of OA progression

MMP-13
=collagen<u>ase</u>-3

- In animal models blockade of MMP-13 attenuates OA progression
- Human trials were terminated because of “off-target” toxicity

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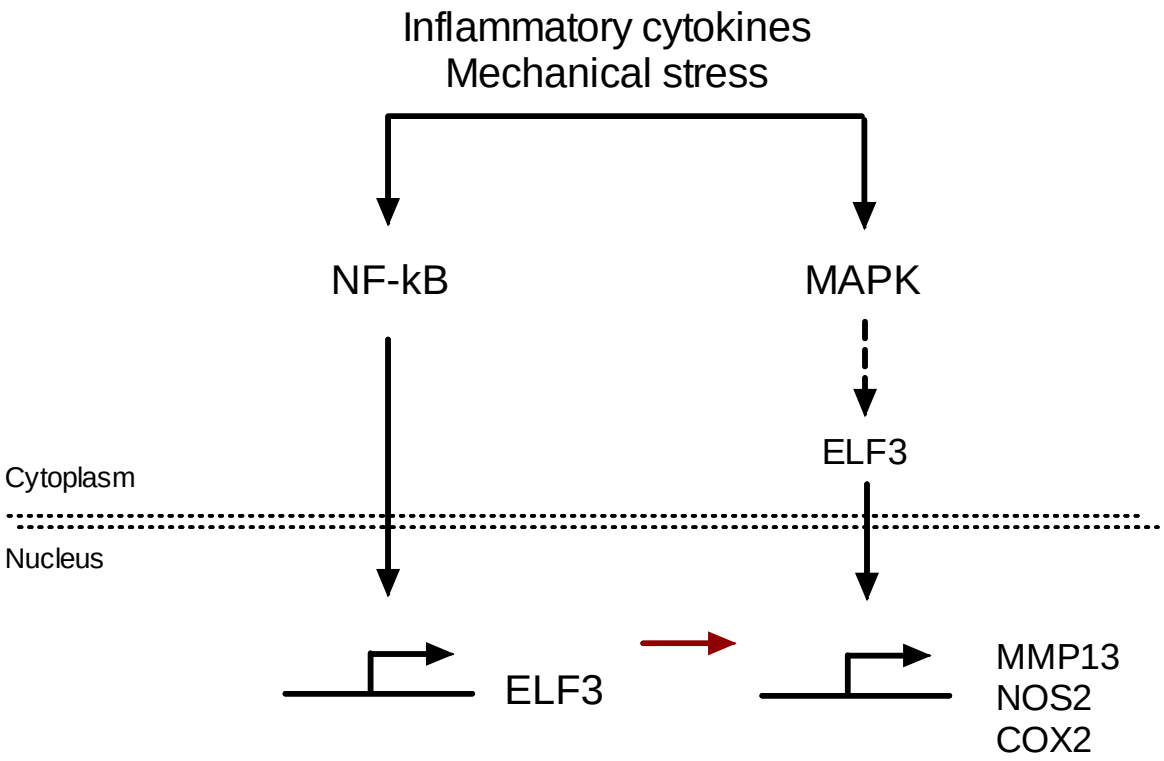
Elf3 regulates proinflammatory and catabolic mediators in chondrocytes



(Sharrocks 2001; Rudders 2001; Eckel 2003; Grall 2005; Kopp 2007; Wu 2008; Peng 2008; Otero 2012; Longoni 2013)

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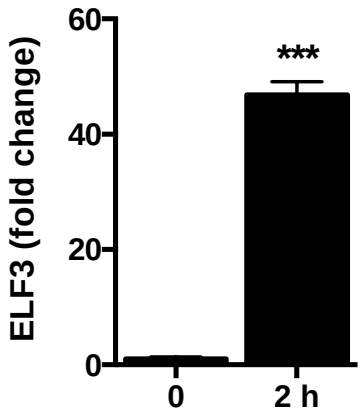
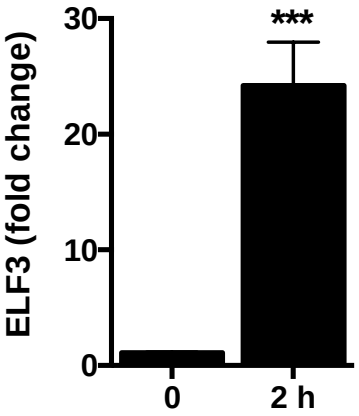
Increased Elf3 mRNA levels in chondrocytes treated with IL-1β



Human primary chondrocytes



Mouse primary chondrocytes

(Adapted from Otero et al., 2012)

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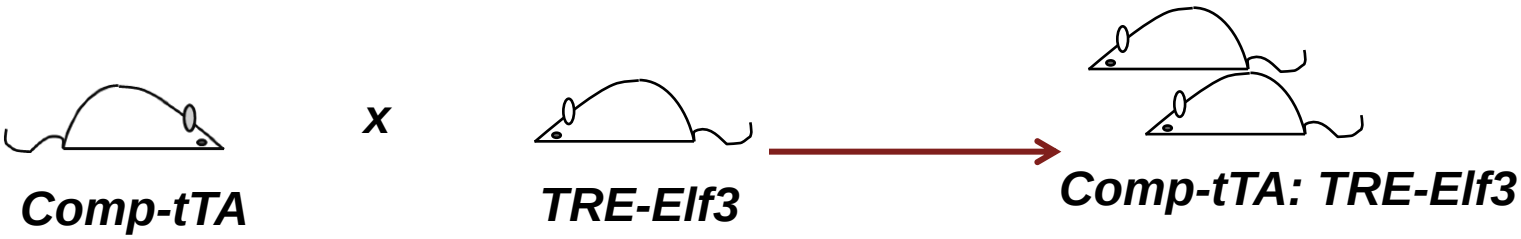
Role of Elf3 in vivo?

Cartilage-specific deletion of Elf3

–>Attenuation of OA in surgically induced (DMM) model

COMP-driven (Tet-OFF) overexpression of Elf3 in synovium and cartilage



–>exacerbation in DMM model

Elisabeth Wondimu,
Miguel Otero, Kirsty Culley, Darren Plumb, et al.

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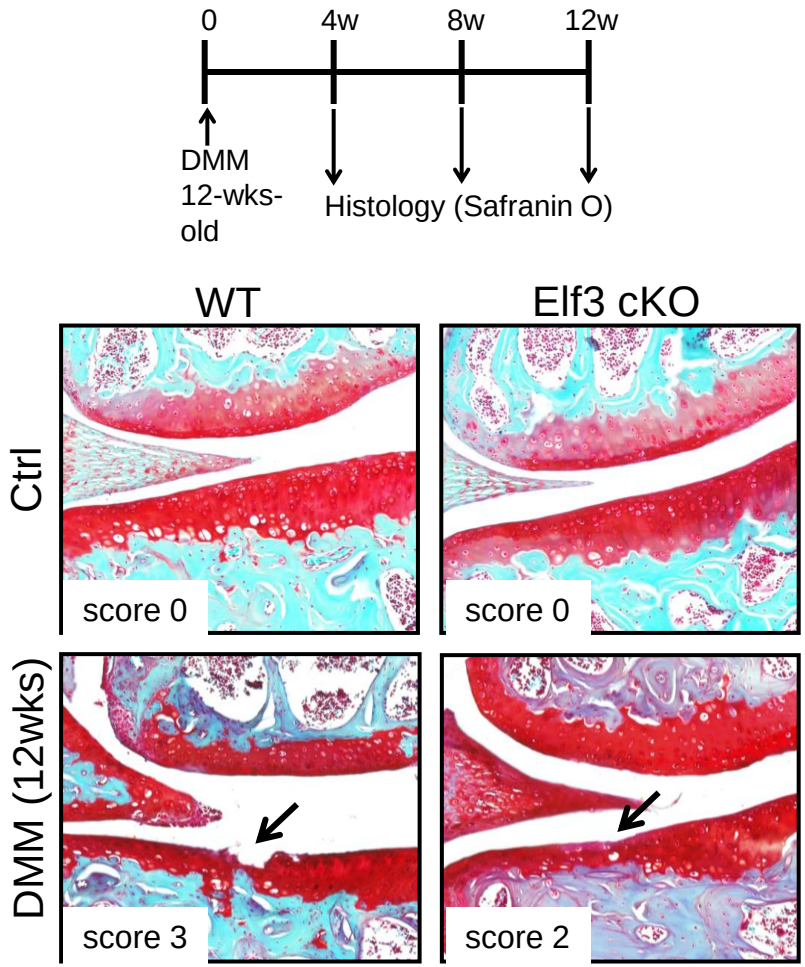
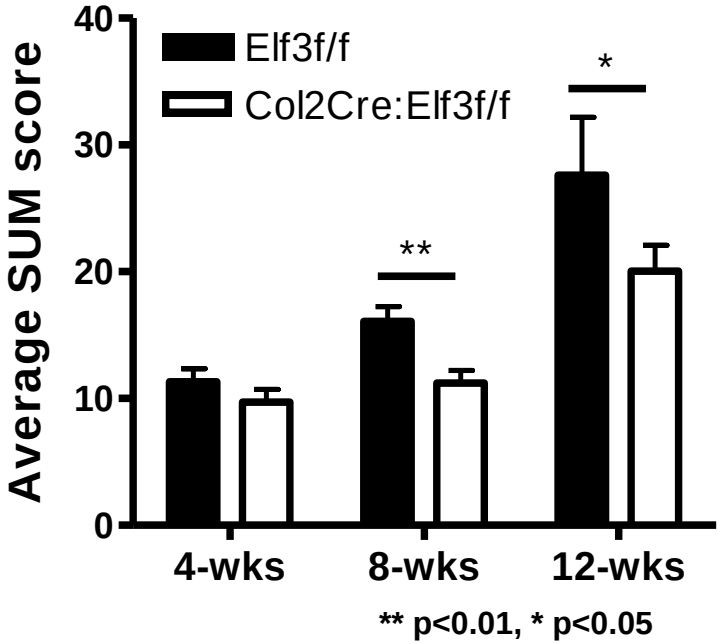
Attenuation of DMM-OA in mice with cartilage-specific Elf3 cKO





No change in osteophyte formation

Elisabeth Wondimu, Miguel Otero, Darren Plumb, et al.

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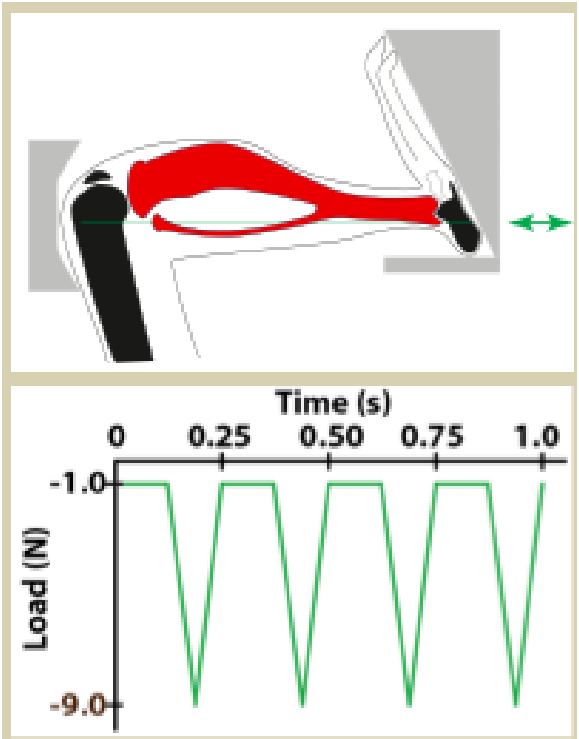
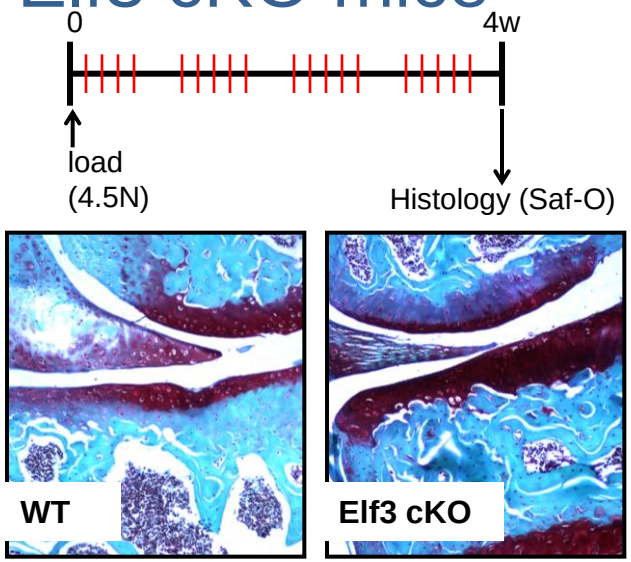
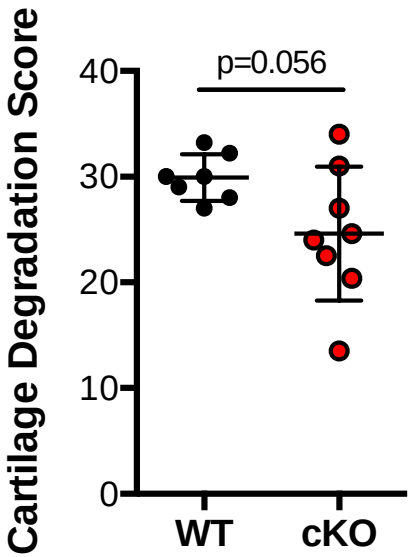
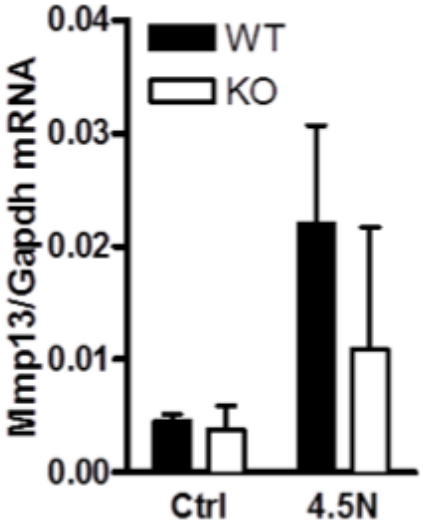
: Attenuation of OA pathology in Elf3 cKO mice









- Cartilage loss
- Subchondral cortical thickening
- Changes are topographically associated

Ko, et al. Arthritis Rheum 2013; 65:1569-78
Ko et al., J Orthop Res. 2016 [Epub ahead of print]

Vinny Craveiro (HHMI/OREF), Mathias Bostrom, Marjolein van der Meulen, et al.

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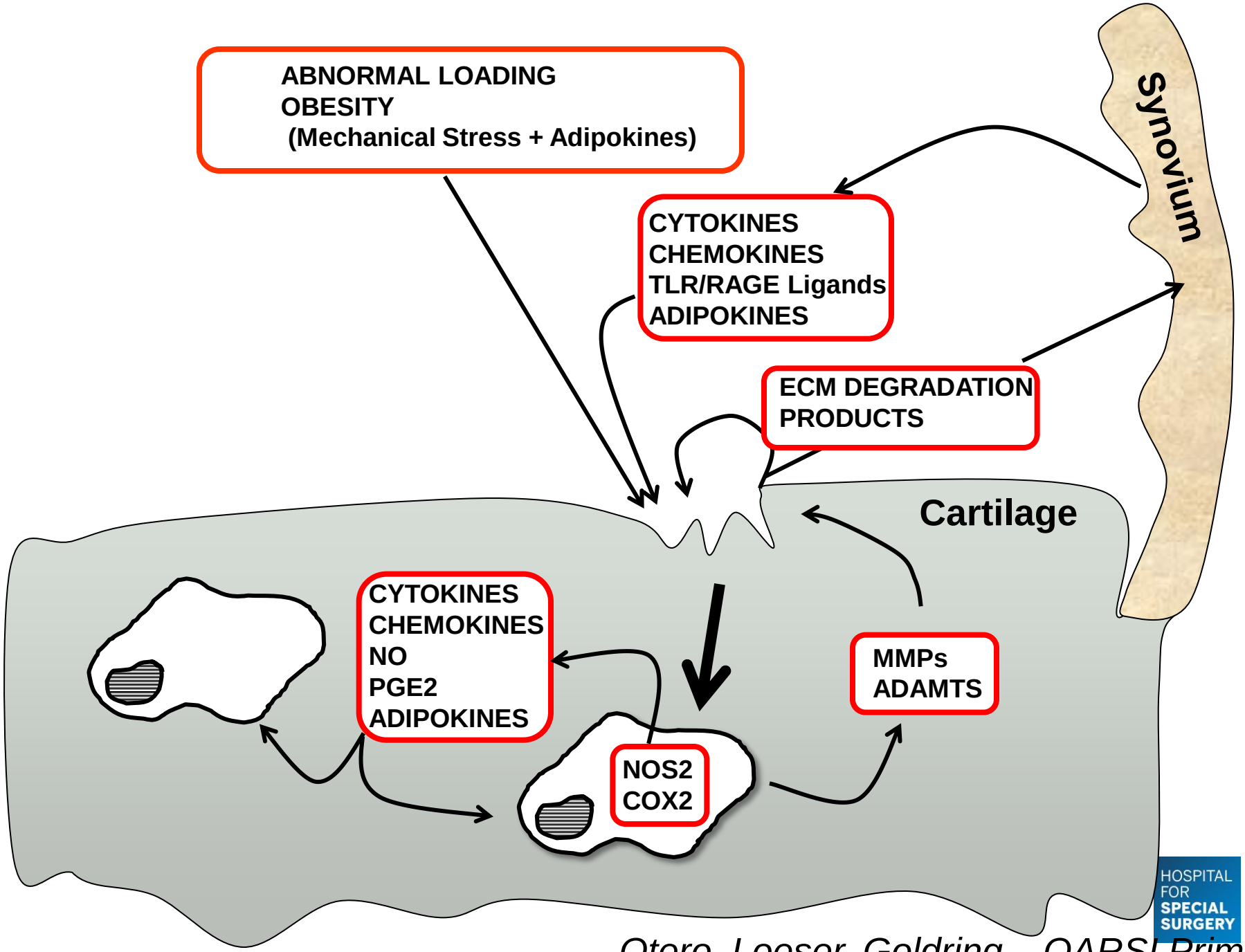

Otero, Loeser, Goldring – OARSI Primer

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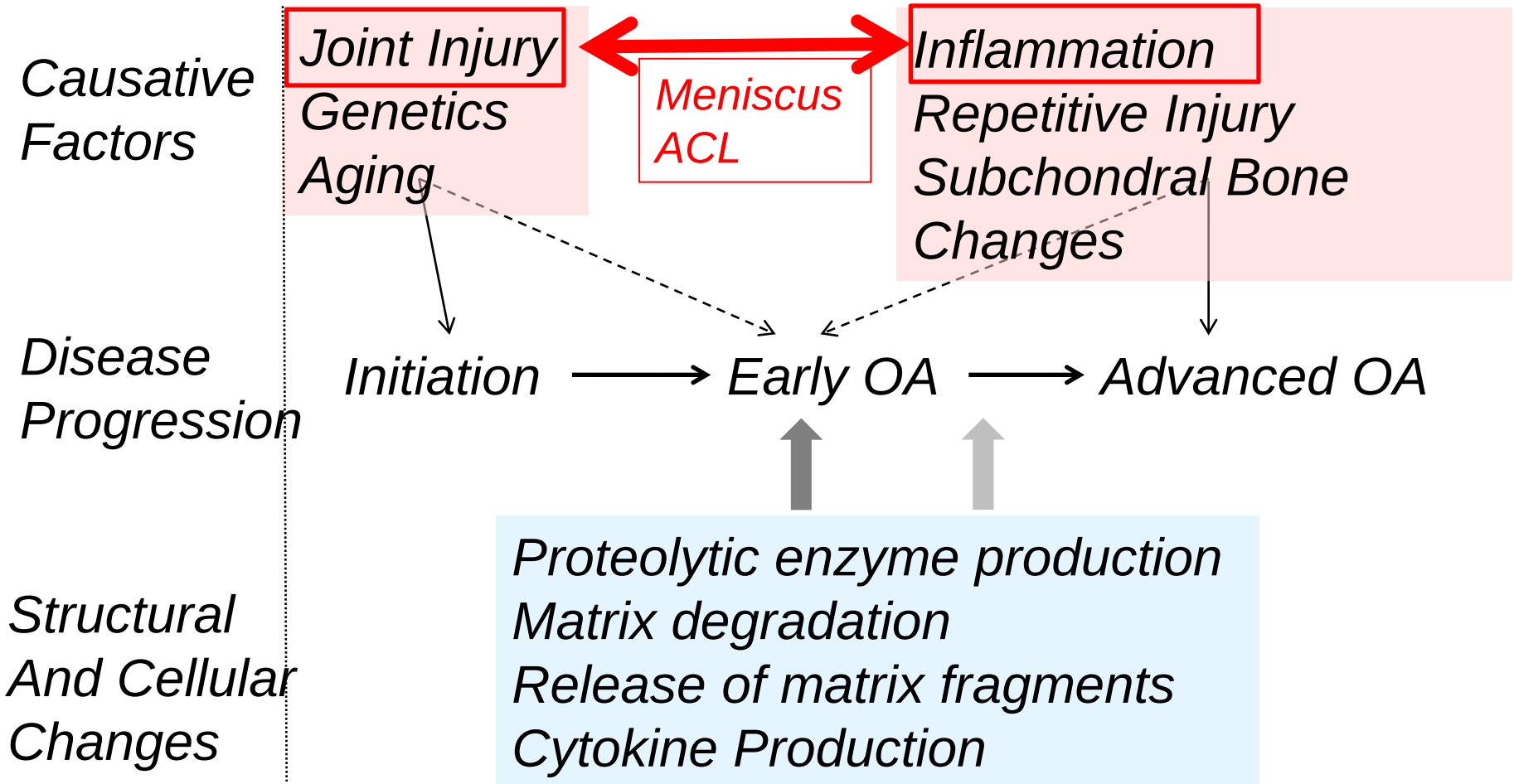
Heterogeneity of OA



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OA: Therapeutic Challenge

- OA is not a homogeneous disorder
- The pathogenic mechanisms differ among individuals
- In the same individual, pathogenic mechanisms and processes may differ at specific stages of disease progression
- Rational approaches to therapy require knowledge of the stage of OA progression and the pathogenic events and processes that determine disease Initiation and progression

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Goldring Lab
Miguel
Vinny
Gary
Justin
Mary
Kirsty
Elisa

Acknowledgements: Collaborators

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- NIH-RC4 AR060546: “Defining Common Molecular Parameters for Onset and Progression of Osteoarthritis”
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  - Yefu Li (Harvard Medical School)
  - Roland Wolkowicz (San Diego State Univ)
- NIH-R21 AR054887: “Epigenetic Regulation of MMP-13”
  - Ko Hashimoto (Tohoku Univ, Sendai, Japan)
  - Richard Oreffo (Trudy Roach), et al. (Univ of Southampton)
- NIH-R21-AR064034-01A1: Marjolein van der Meulen (Cornell Univ) :: “Role of Cartilage Matrix in a model of load-induced OA”
- Carl Blobel (HSS): Arthritis Foundation IRG-6353: “Role of iRhom2 and ADAM17 in osteoarthritis”
- Eleonora Olivotto
  - University of Bologna
- Marta Favero
  - University of Padova

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