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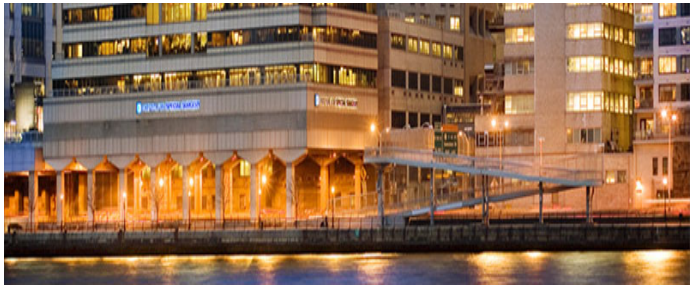
Mechanisms of Cartilage Damage

Mary B. Goldring, PhD



Senior Scientist, Hospital for Special Surgery, New York, NY
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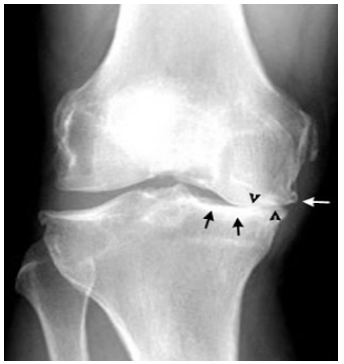
WEILL CORNELL MEDICAL COLLEGE · CORNELL UNIVERSITY

Osteoarthritis (OA)

•Most common cause of disabilities in older population
• > 20 million Americans affected by OA
• More than 900,000 joint replacements every year at a cost of $42.3 million



• Symptoms: Pain and stiffness, swelling and tenderness
• Radiographic signs: joint space narrowing, osteophyte formation, bone marrow lesions

• Treatment options: Control of pain and inflammation, improvement of joint function, and ultimately surgery

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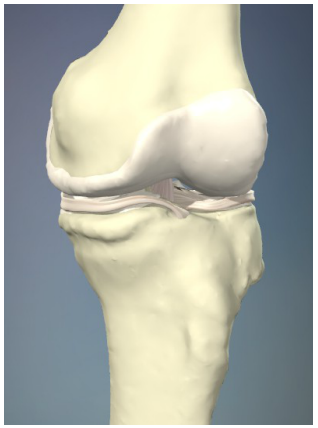
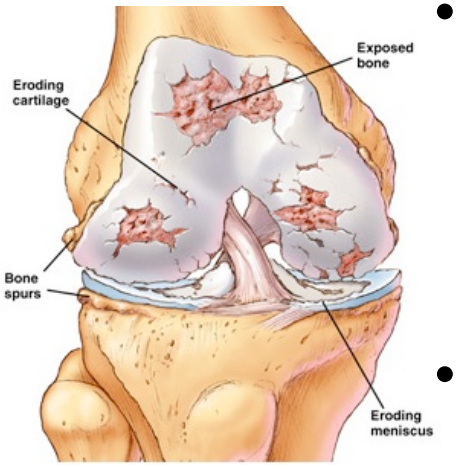
OA is a "joint" disorder



- 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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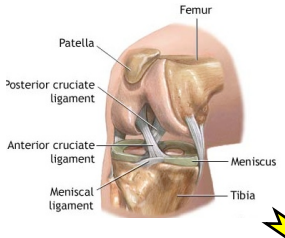
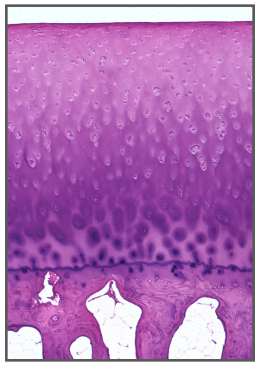
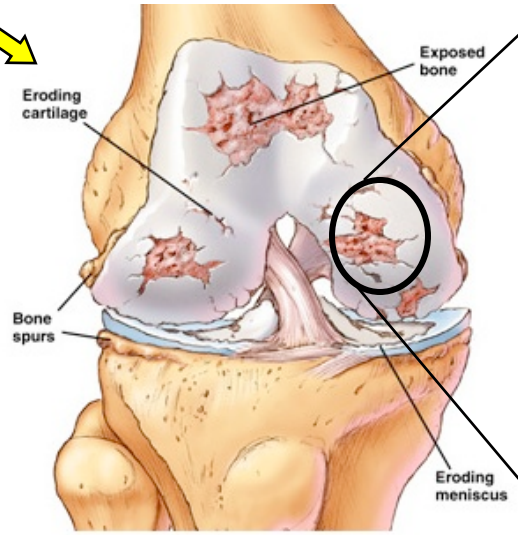
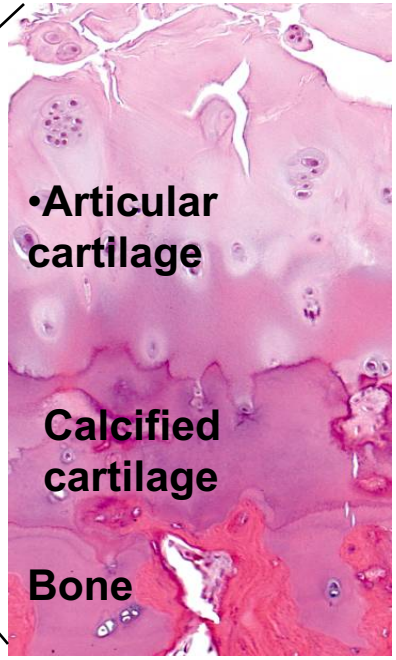
Cartilage & Osteoarthritis





normal





- •Fragmentation and fissuring of cartilage matrix
- •Local chondrocyte proliferation and cell death
- •Increased cartilage degrading activity and altered synthetic activity
- •Cartilage calcification and tidemark advancement
- •Vascular invasion from subchondral bone

- •The complexity of the composition and cellular organization of articular cartilage presents a tissue engineering challenge for developing repair strategies
- • Successful therapies must prevent damage or promote repair to recapitulate the physiological and functional properties of cartilage.

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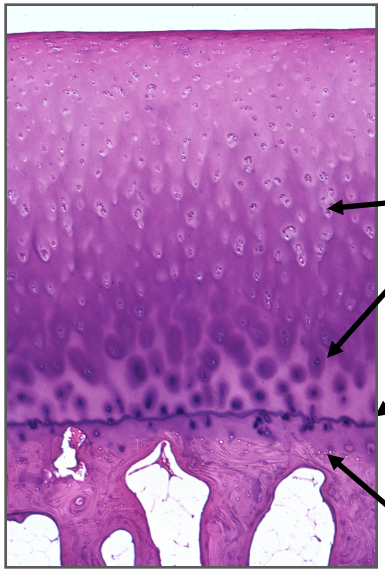
Normal articular cartilage

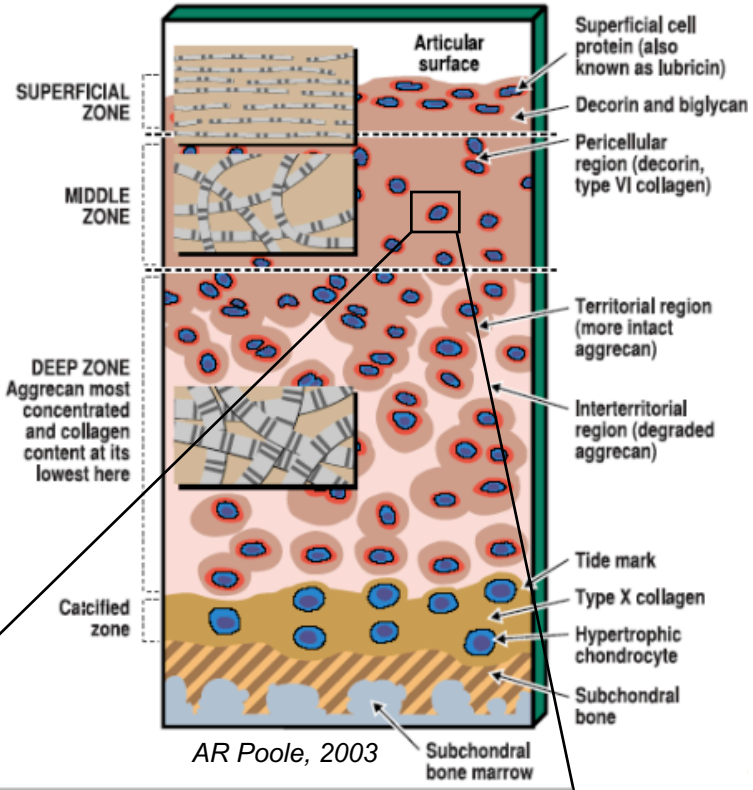


Chondrocytes

Tidemark

Calcified cartilage

Subchondral bone



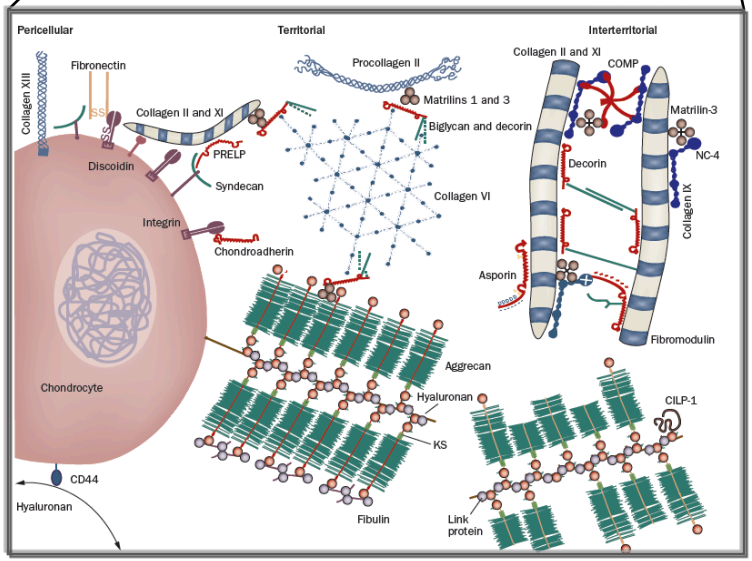
AR Poole, 2003

Chondrocyte

Degradation

Repair

Low turnover maintenance of cartilage Matrix



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

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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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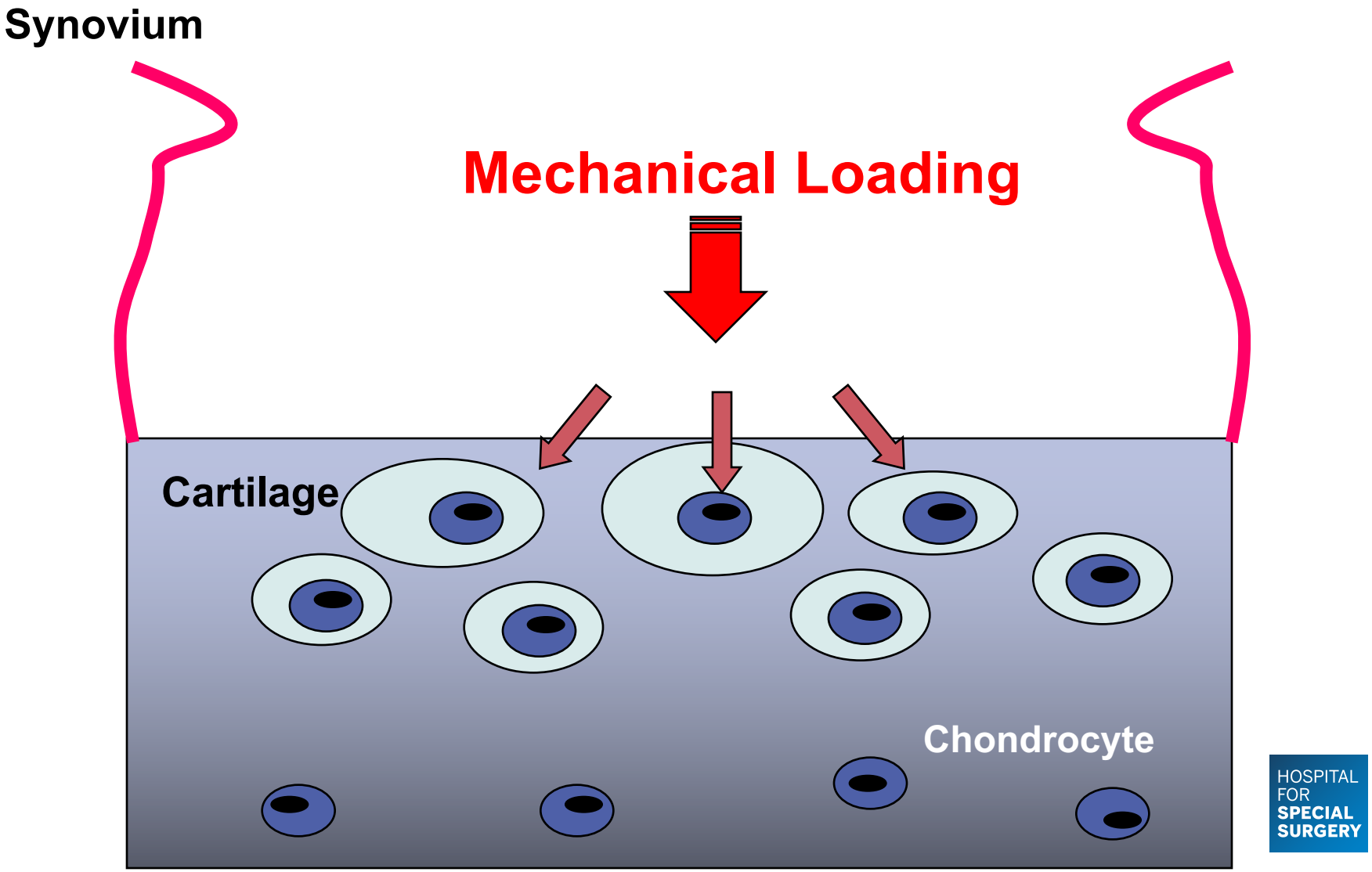
Adaptation of chondrocytes to physiological mechanical loading



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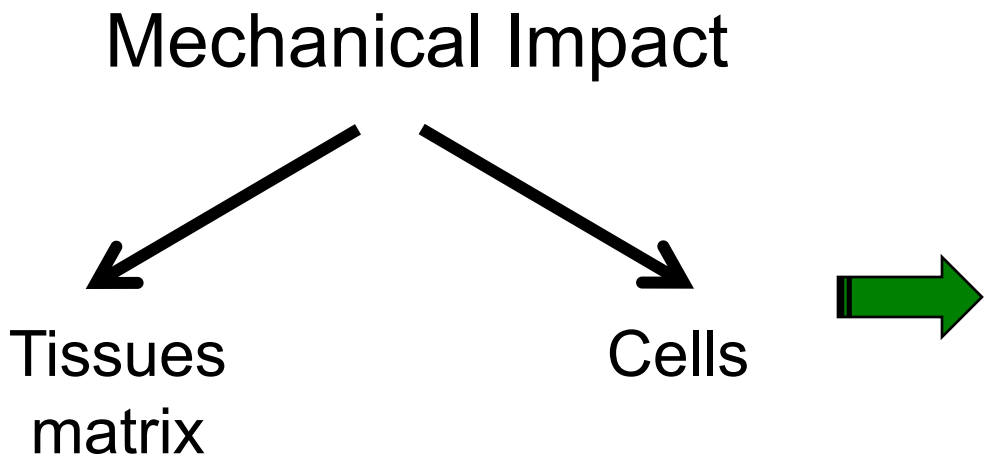
Physiological mechanical loading

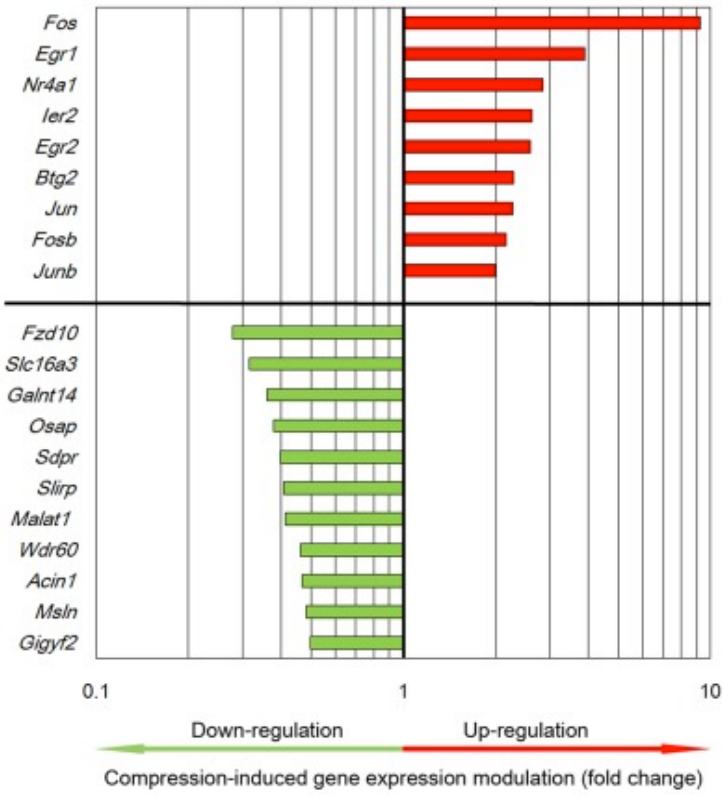


Maintenance and/or restoration of composition and structural and function properties of the tissue matrix

How do chondrocytes sense their mechanical environment?

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

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



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

Implications: Targeting mechanosensors represents a rationale approach for OA therapy

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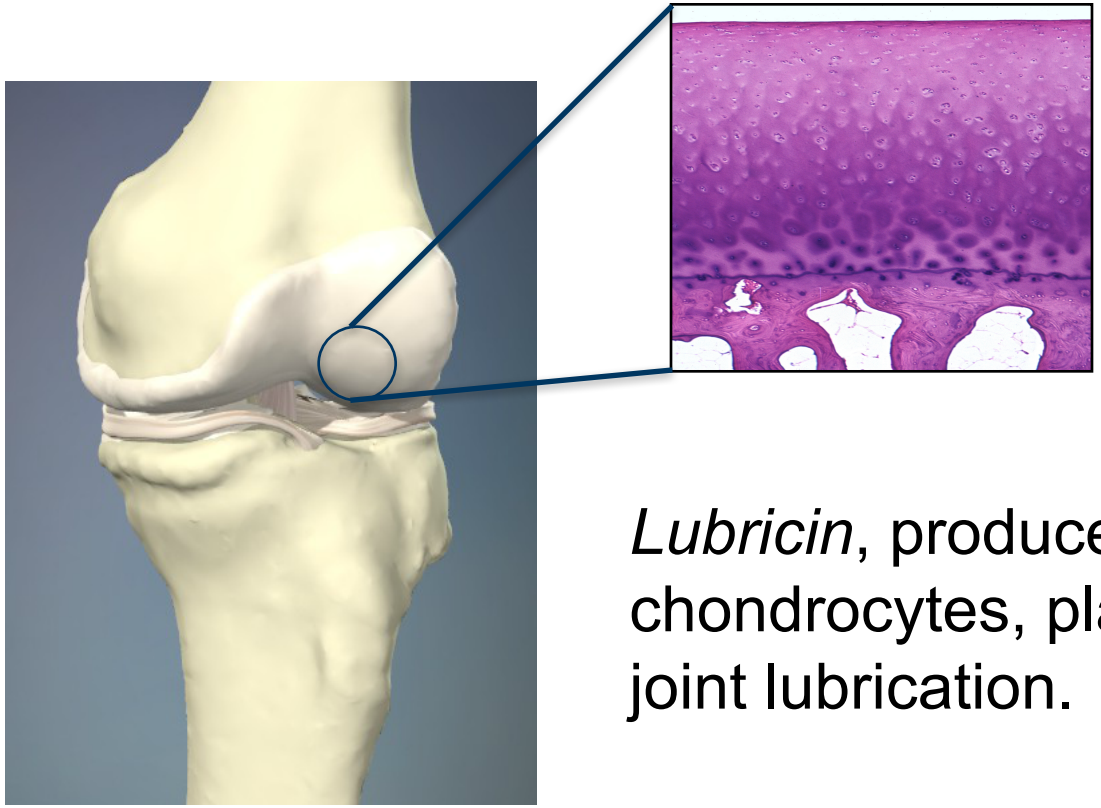
Mechanism of joint “lubrication”: Role of *lubricin*

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



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

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Role of *lubricin* in cartilage homeostasis

- 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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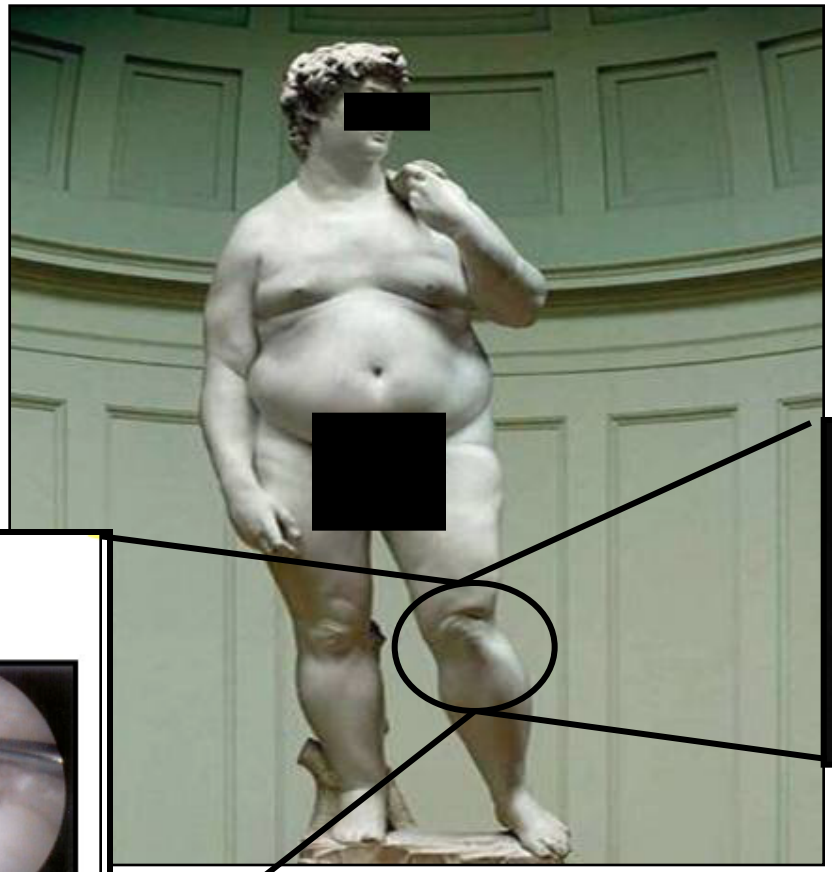
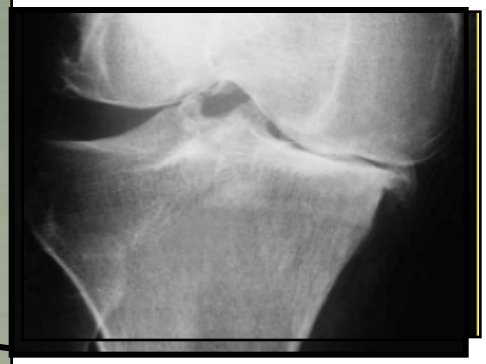
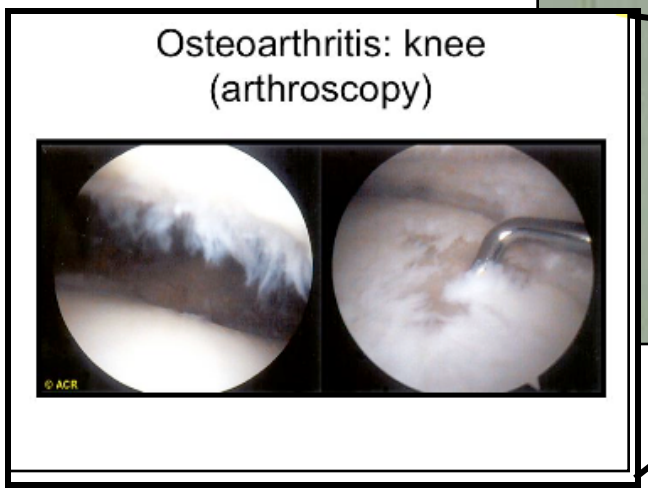
Michelangelo's David: the late years

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







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

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Age-associated changes in chondrocytes

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

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

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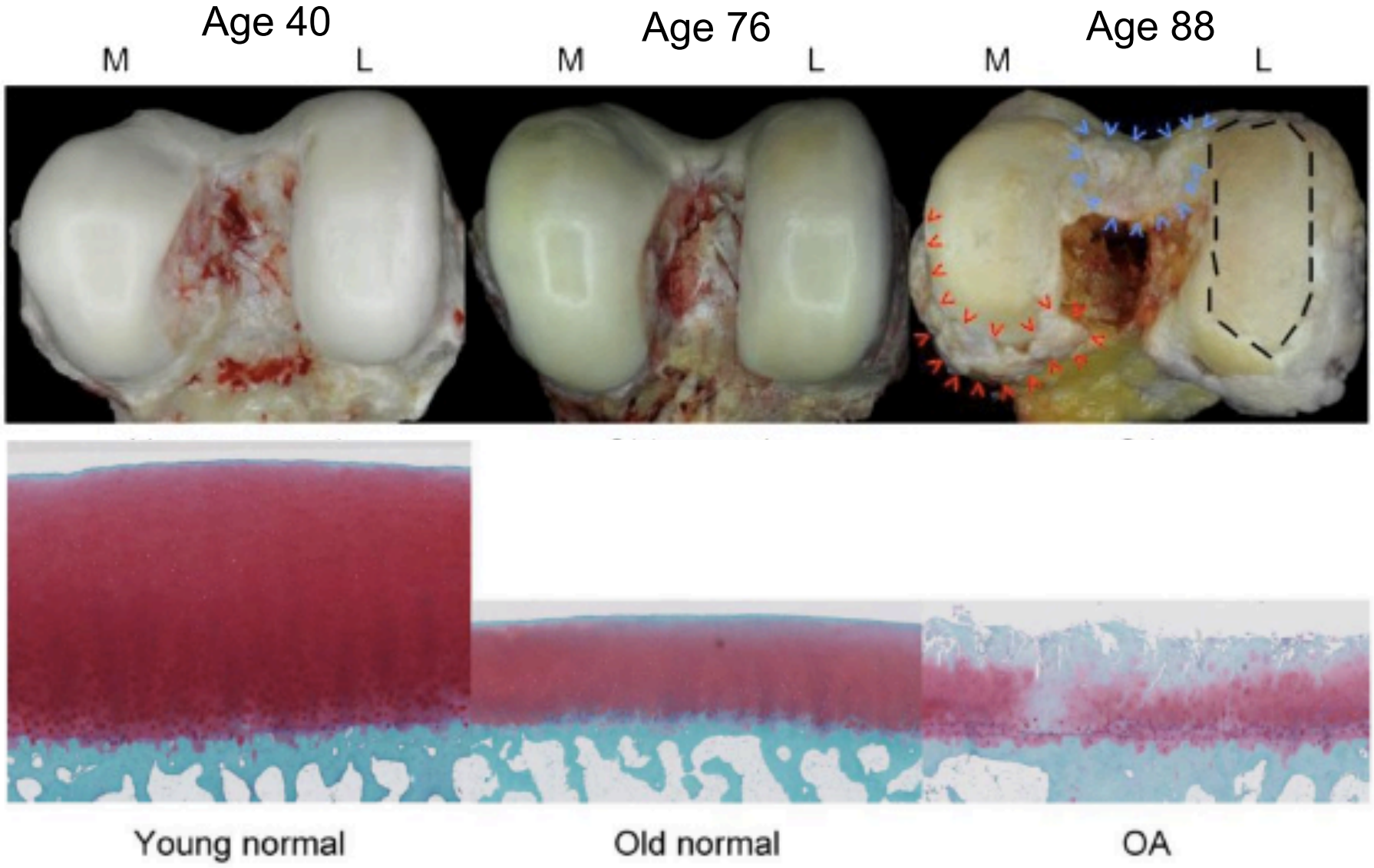
Macroscopic and Histological Appearance of Human Articular Cartilage



Lotz M & Loeser RF: Bone 2012

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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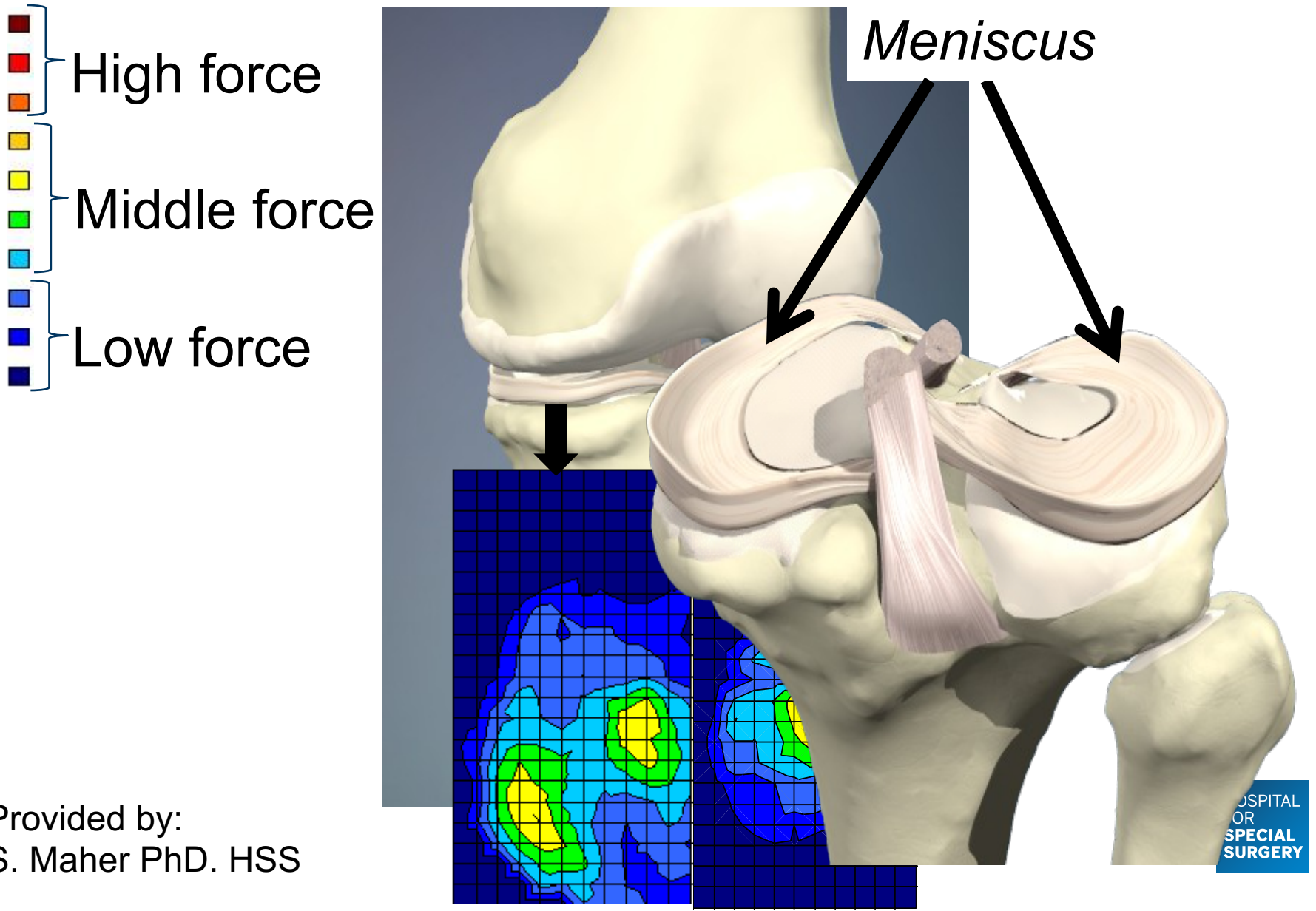
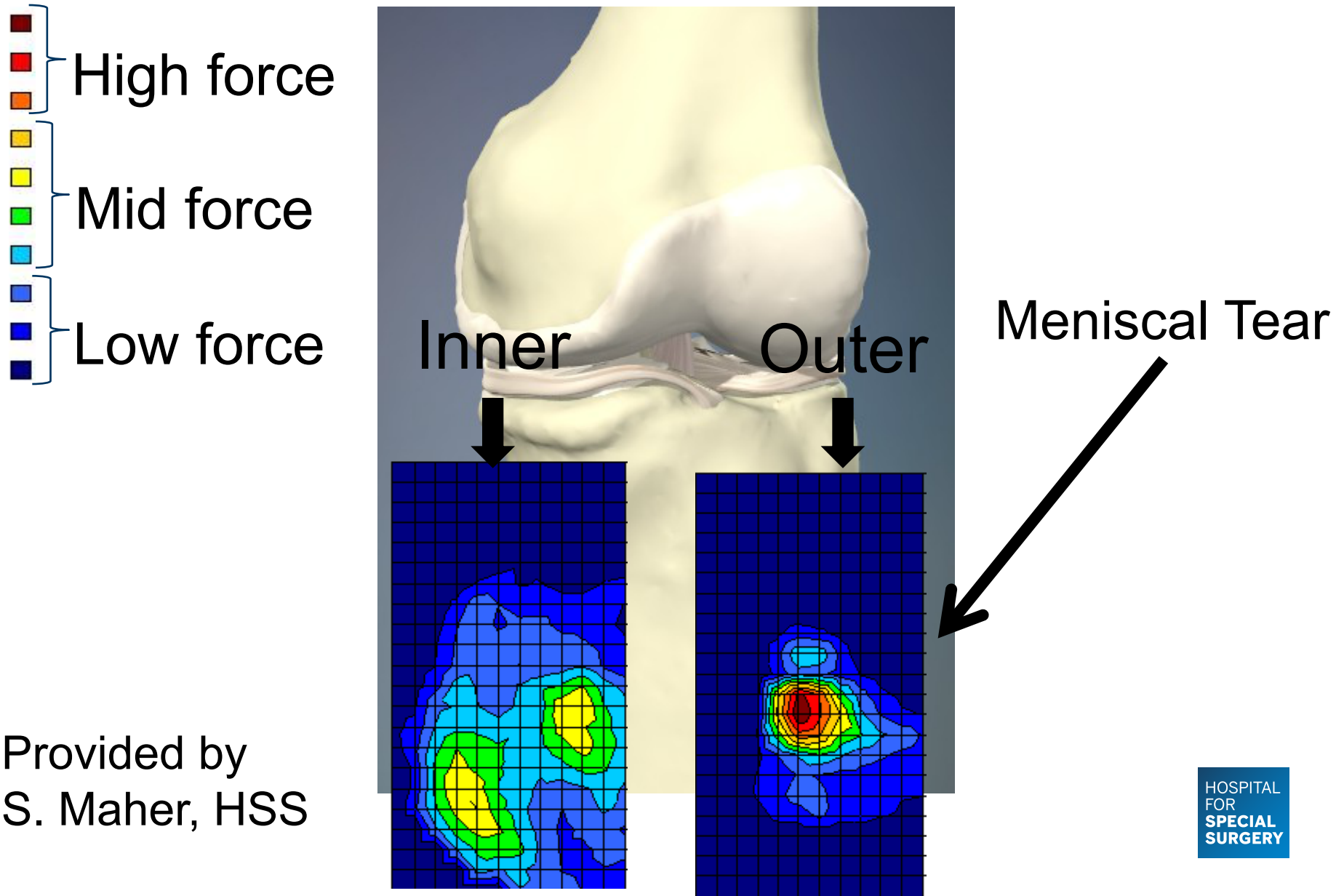
Distribution of contact forces in the knee



Provided by:
S. Maher PhD. HSS

Meniscal tear disrupts contact forces



Provided by
S. Maher, HSS

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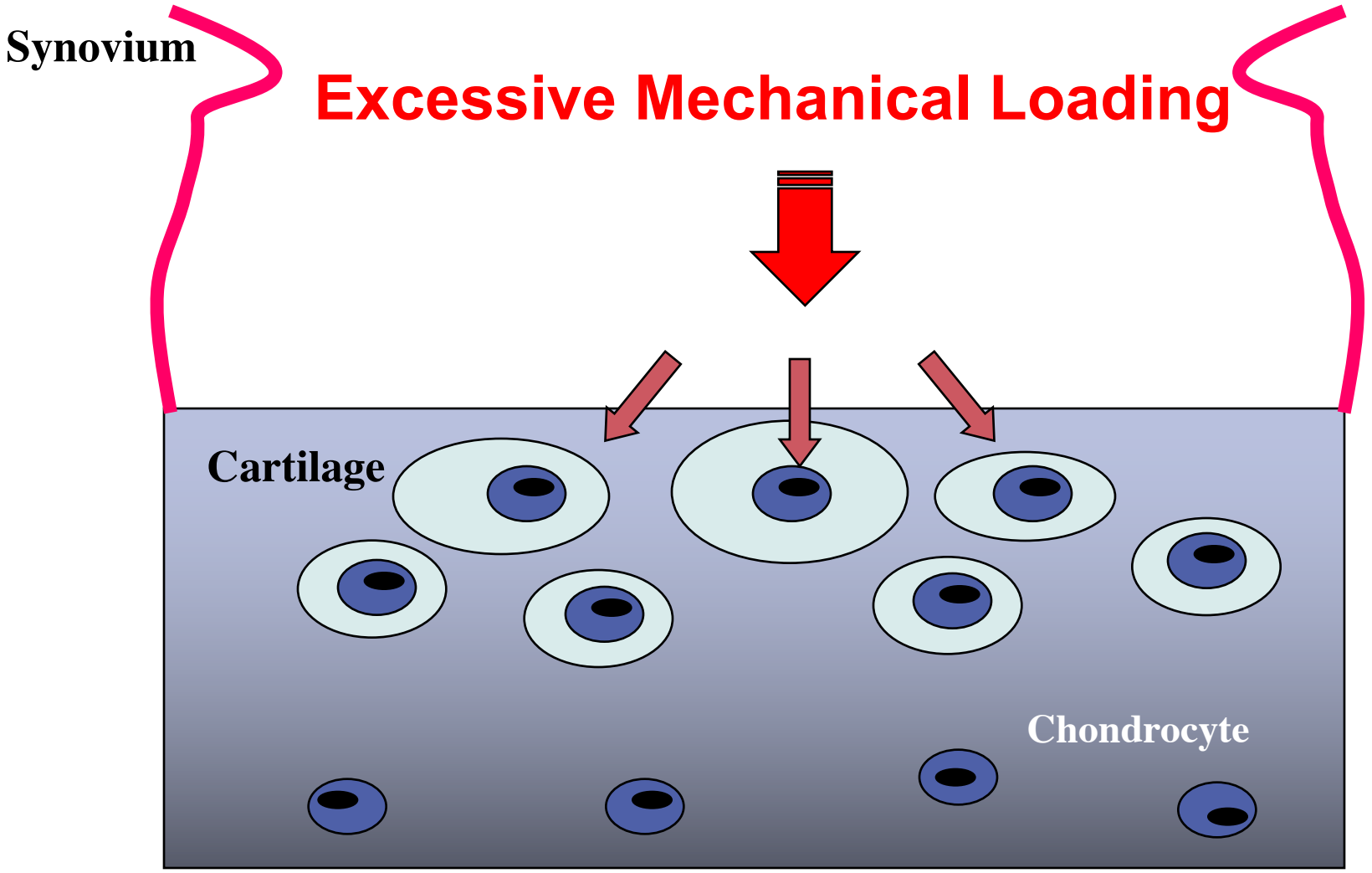
Excessive mechanical loading leads to irreversible dysregulation of chondrocyte function



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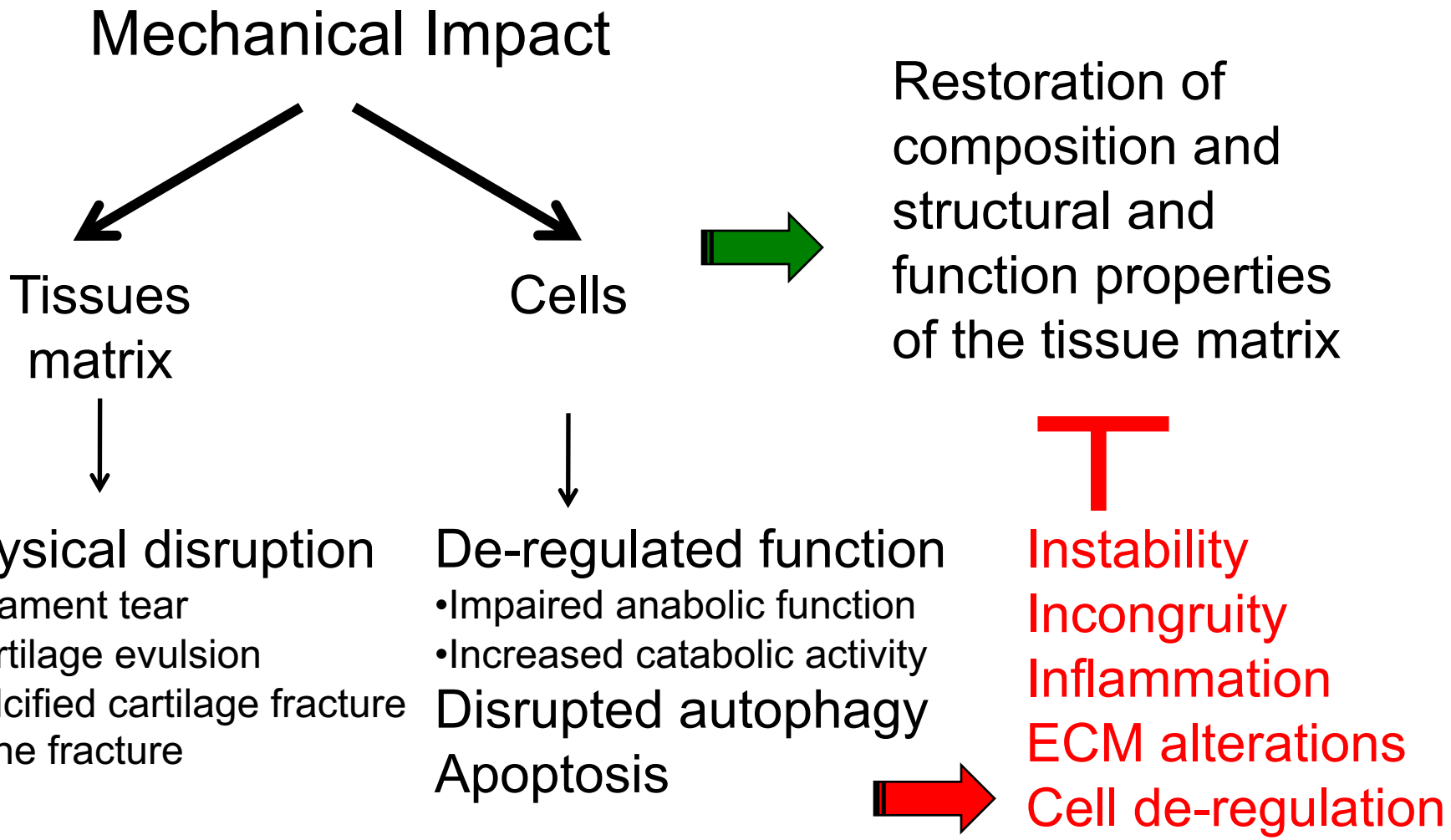
Mechanical injury



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 or response to 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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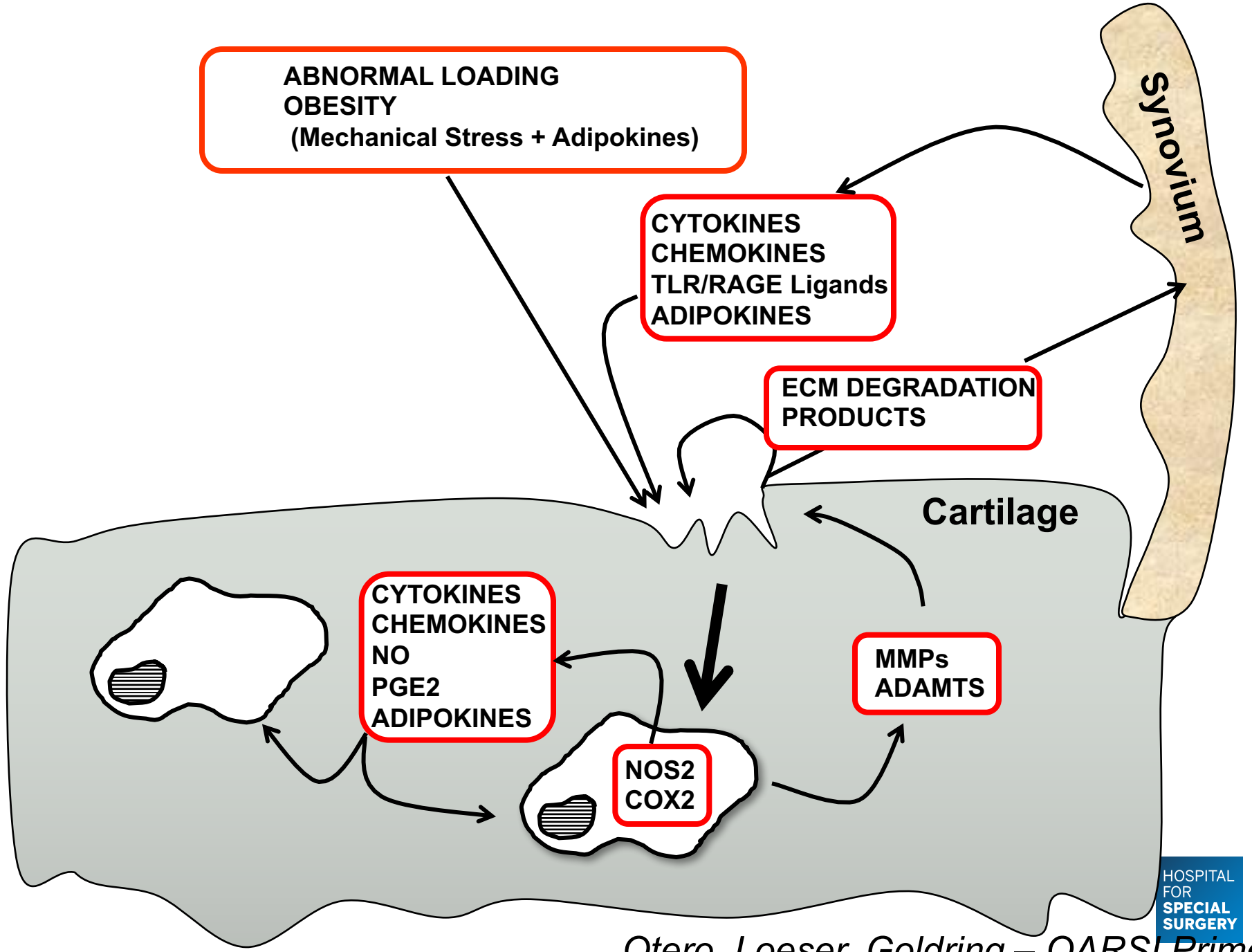

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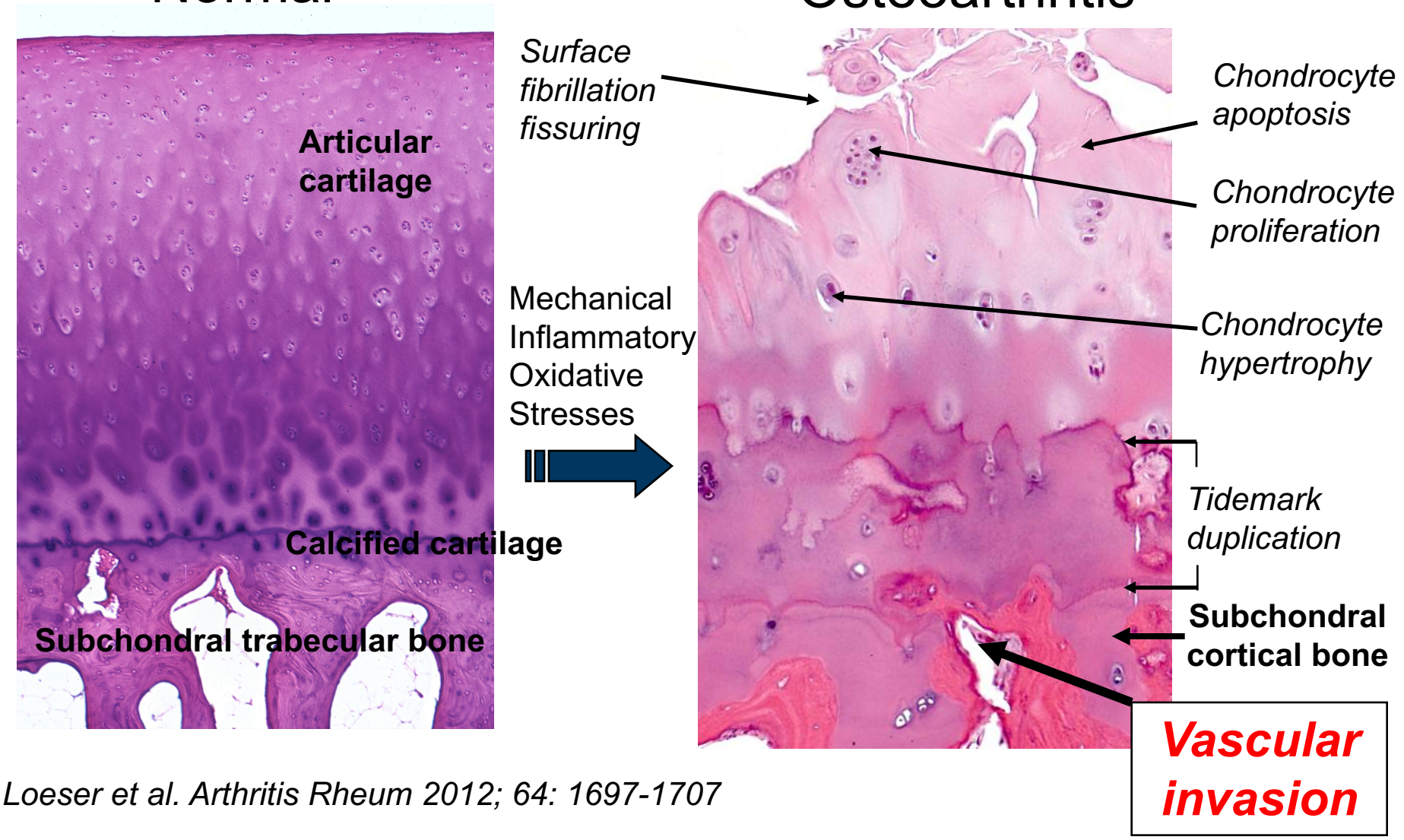
Otero, Loeser, Goldring – OARSI Primer

From homeostasis to osteoarthritis



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

Structural organization of the osteochondral unit

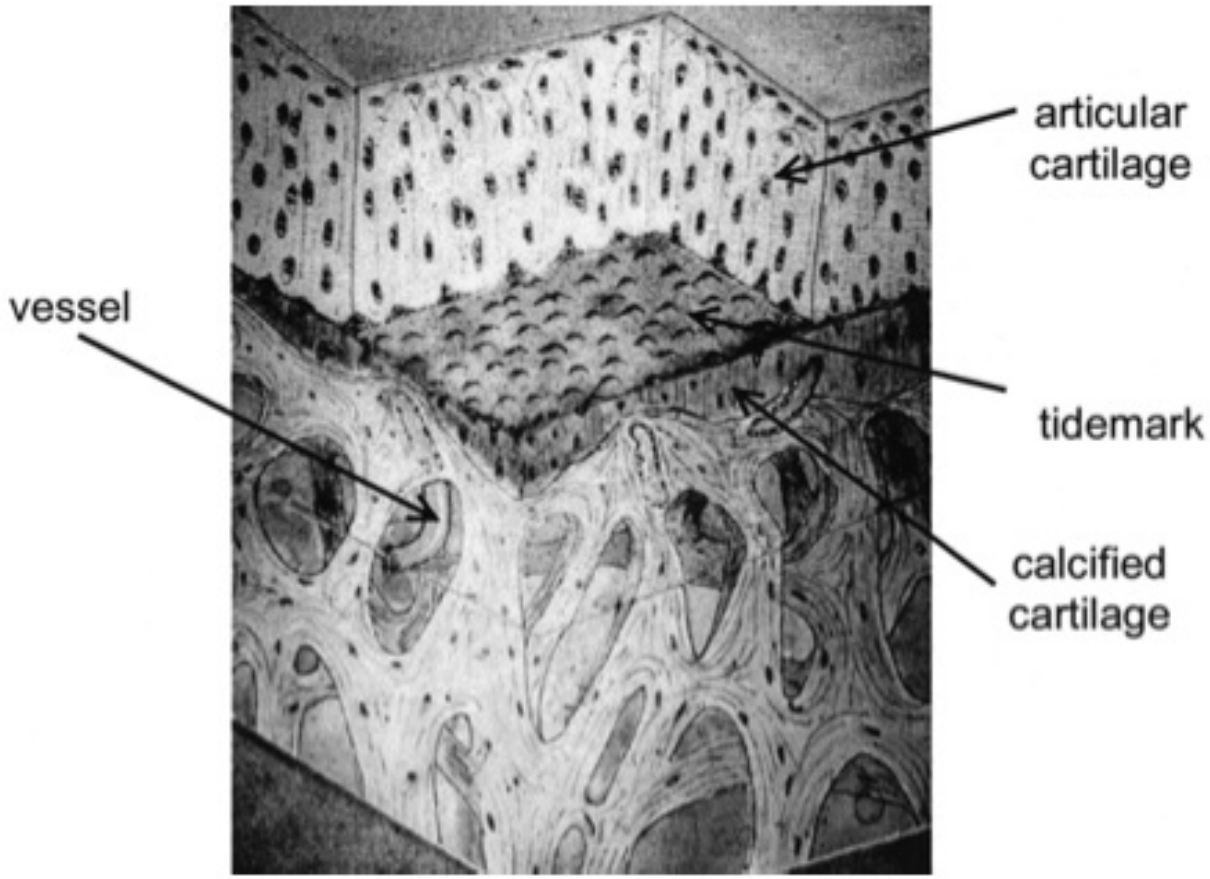
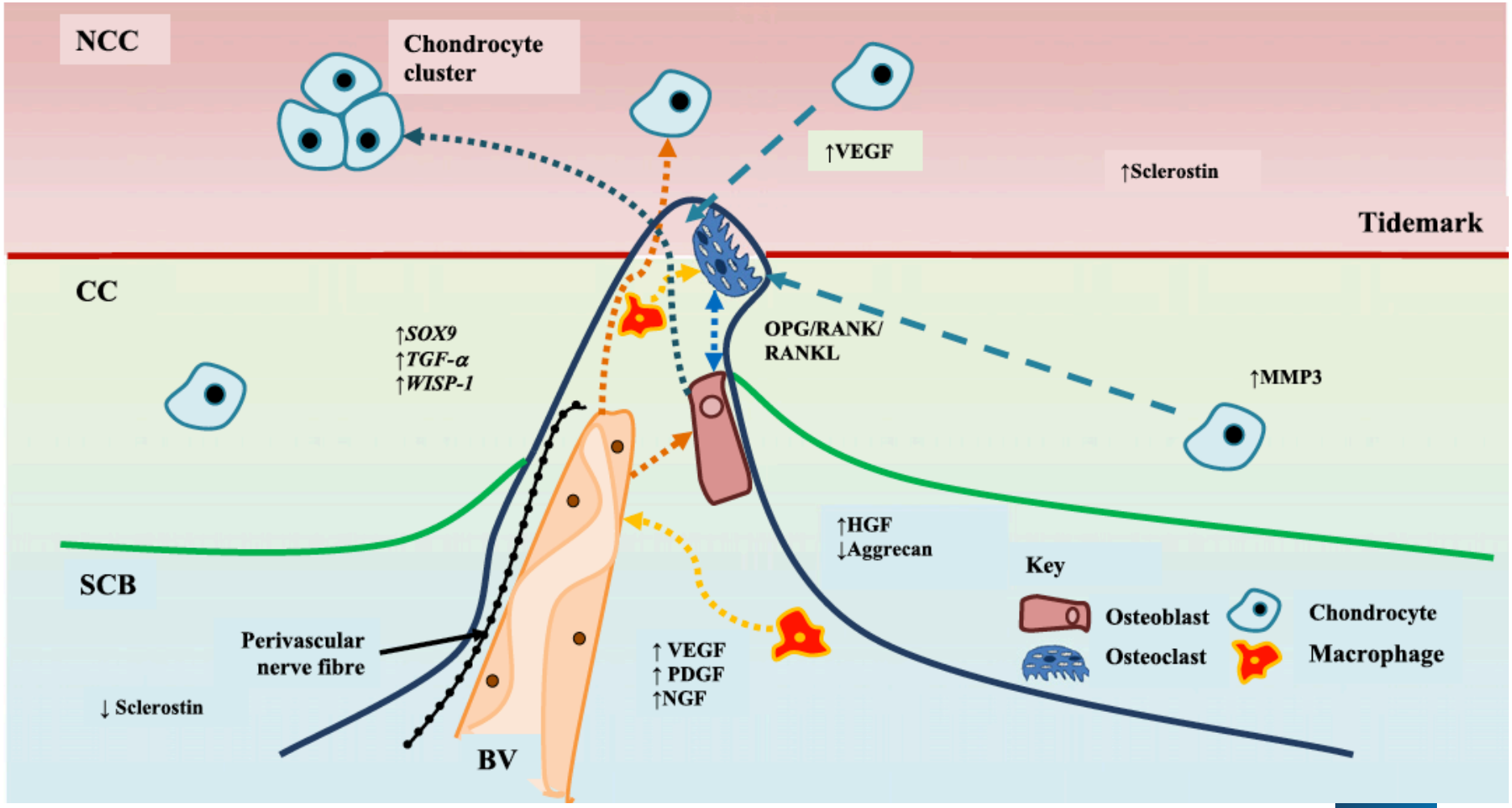


Diagram of the bone surface with noncalcified cartilage cut away to reveal the calcified cartilage. (Reprinted from Bullough and Jagannath, 1983[13], with permission from The British Editorial Society of Bone and Joint Surgery, London, UK.)

Molecular cross-talk at the osteochondral junction



Suri S, Walsh DA. Bone 2012;51(2):204-11

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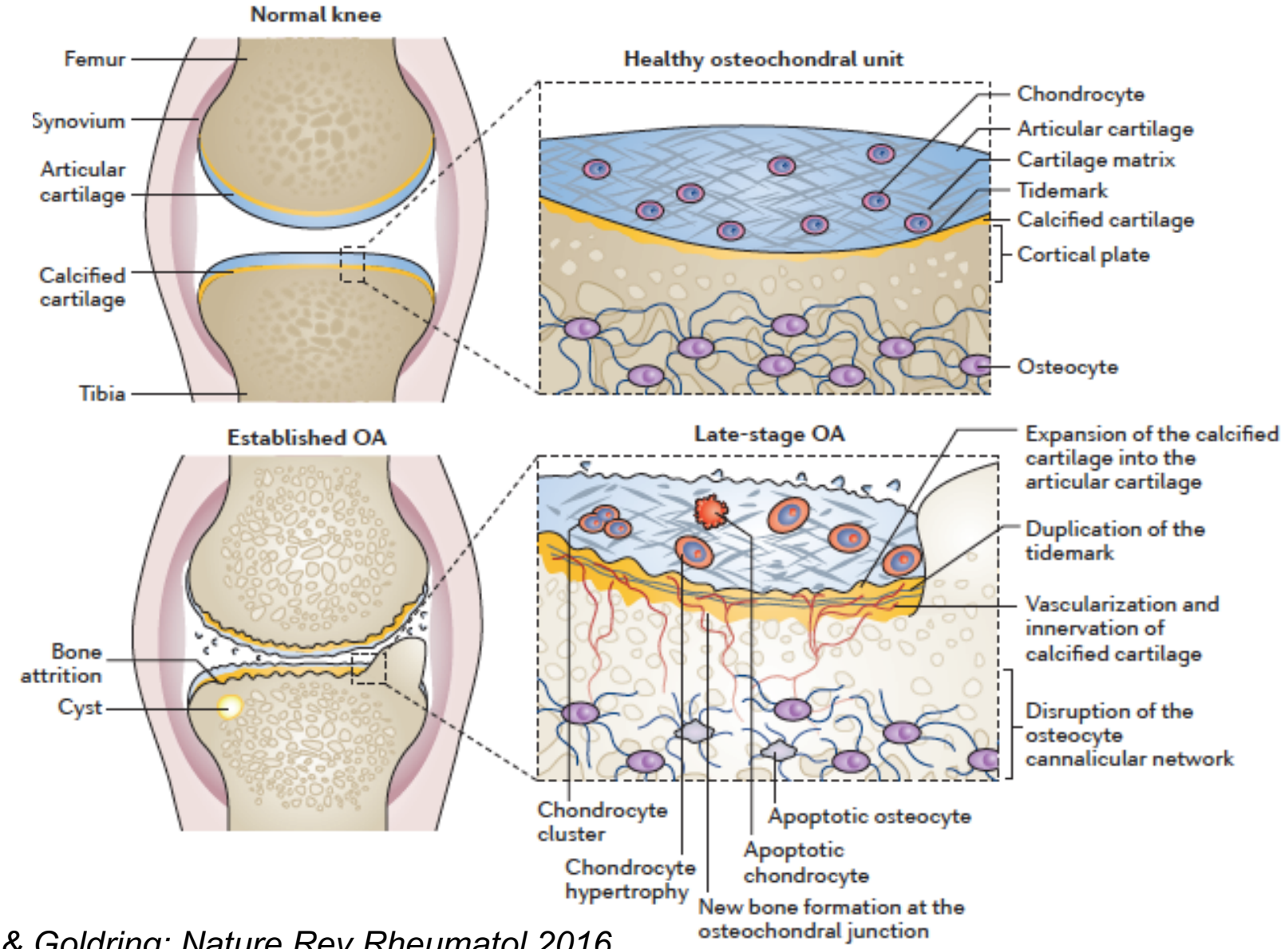
Structure of the normal knee joint and the osteochondral unit and changes in late-stage OA



Goldring & Goldring: Nature Rev Rheumatol 2016

OA pathogenesis: Current View

- 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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Goals of OA Therapy

- Make diagnosis early before significant structural damage and symptomatic and functional impairment
- Control symptoms and maintain function
- Prevent progression
- Monitor clinical course and treatment response
- Minimize adverse therapeutic side effects

Modified from OARSI recommendations for the management of hip and knee OA
Zhang W et al. Osteoarthritis and Cartilage. 2008. 16: 137-162

Bottom line: There isno approved pharmacologic therapy that has been shown to prevent the development or progression of OA.

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Pharmacologic (Symptomatic) treatment of OA

- **Oral**
  - Acetomenophen
  - NSAIDs
  - COX-specific inhibitors
  - Glucosamine/chondroitin sulfate
- **Intraarticular**
  - Glucocorticoids
  - Hyaluronan
  - Platelet Rich Plasma (PRP)
- **Topical**
  - Capsaicin
  - Methylsalicylate

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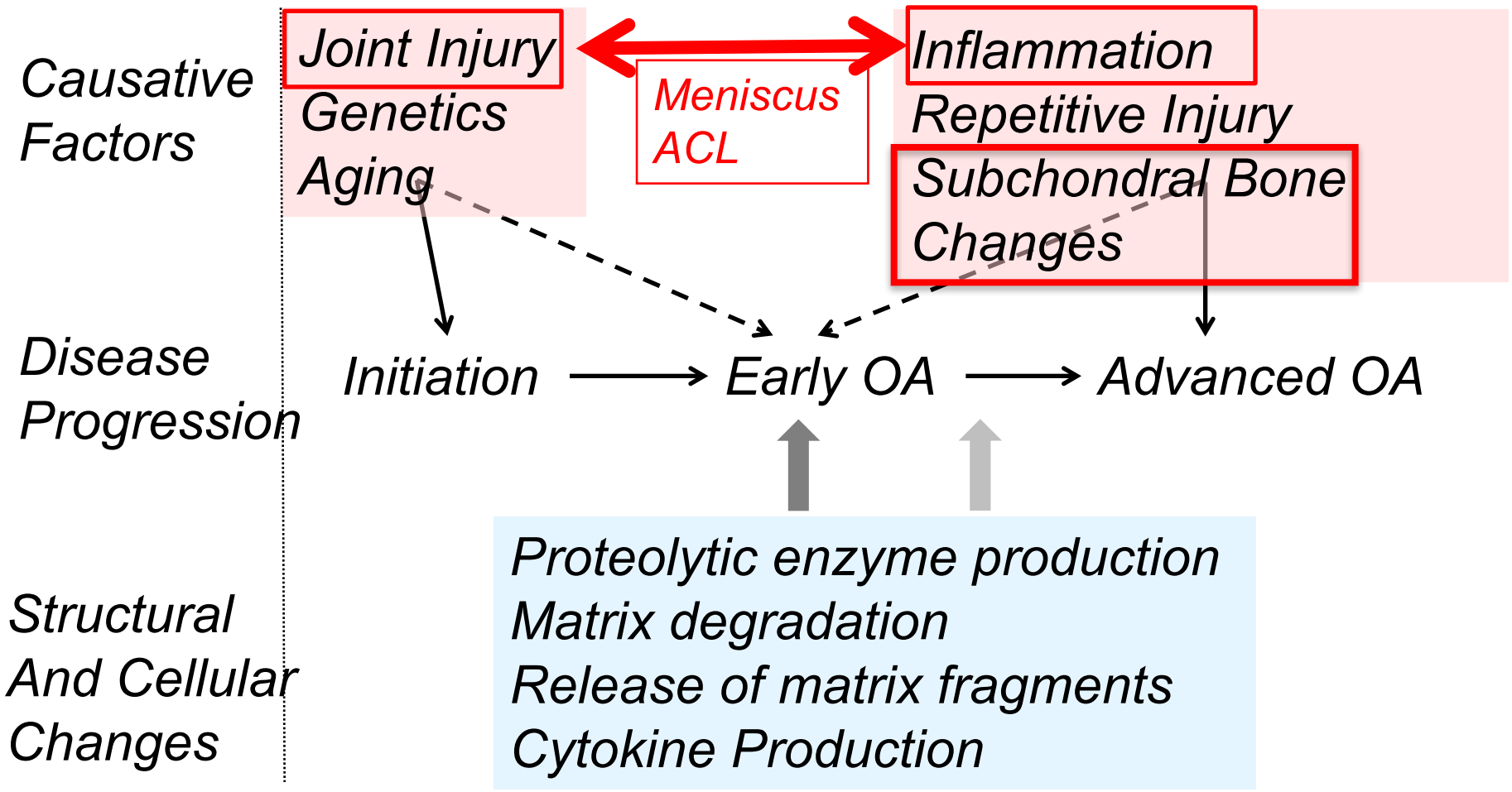
Heterogeneity of OA



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Cpnclusions: OA as a 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 initiation and progression.
- Knock out of a number of different genes can decrease OA development in mouse models. Therefore, it is difficult to determine which mechanisms to target for therapy.
- The design of clinical trials with selection of cohorts based on risk factors may lead to more rational approaches to therapy targeting disease initiation and progression.

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Kirsty
Mary
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  - Yefu Li (Harvard Medical School)
  - Roland Wolkowicz (San Diego State Univ)
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  - Richard Oreffo (Trudy Roach), et al. (Univ of Southampton)
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