Structure and function of Articular Cartilage

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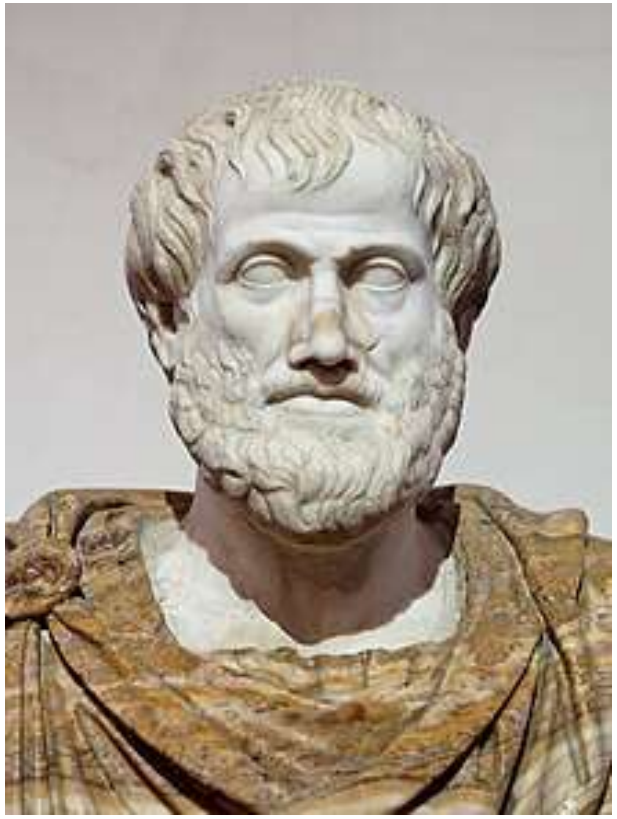
Historical context of articular cartilage

"Cartilage is found where it is an advantage that the solid framework should be pliable and glutinous for the benefit of the flesh that surrounds them. This applies to the ears and the nostrils. Such projecting parts quickly get broken if they are brittle. Cartilage and bone are the same in kind and differ only by 'the more and less'".

Aristotle (4th Century BC)



Aristotle (384 – 322 BC)

Benedek *et al*, 2006, Osteoarthritis and Cartilage

Historical context of articular cartilage

"Cartilages are spread on some parts of them [bones], such as the joints, to make them smooth, and Nature also uses cartilages occasionally as moderately yielding bodies. Cartilage serves as a grease for the joints[2a]." Elsewhere it is not only cartilage but also synovial fluid that protects joints against wear: ". Nature has again searched out a double remedy, first covering each member of the joint with cartilage and then pouring over the cartilages themselves a sort of oily substance, a greasy, glutinous fluid, which gives every joint an easy movement and protection against wear[2b].""".

Galen (3th Century AD)

Galen (126 – 219 AD)

Benedek *et al*, 2006, Osteoarthritis and Cartilage

Historical context of articular cartilage

"An articulating Cartilage is an elastic Substance uniformly compact, of a white Colour, and somewhat diaphanous, having a smooth polished Surface covered with a Membrane; harder and more brittle than a Ligament, softer and more pliable than a Bone. We may compare the Texture of a Cartilage to the Pile of Velvet, its Fibres rising up from the Bone, as the silky Threads of that rise from the woven Cloth or Basis. Now these perpendicular Fibres make the greatest Part of the cartilaginous Substance; but without doubt there are likewise transverse Fibrils which connect them, and make the Whole a solid Body, though these last are not easily seen, because being very tender, they are destroyed in preparing the Cartilage.The Perichondrium of the smooth articulating Cartilages is so fine, and firmly braced upon the Surface, that there is room to doubt whether it has been often demonstrated, or rightly understood. Every Joint is invested with a Membrane, which forms a complete Bag, and gives a Covering to every thing within the Articulation. The Blood-vessels are so small, that they do not admit the red Globules of the Blood; so that they remain in a great measure unknown. Nor even by this Method [injection of liquid wax] are we able, in adult Subjects, to demonstrate the Vessels of the true cartilaginous Substance. From the great Insensibility of a Cartilage some have doubted of it being furnished with Nerves; yet, as it is generally allowed, that these are a sine qua non in the Growth and Nourishment of Animals, we have no sufficient Reason to deny their Existence in this particular Part….**an ulcerated Cartilage is universally allowed to be a very troublesome Disease; that it admits of a Cure with more difficulty than a carious Bone; and that, when destroyed, it is never recovered**[11]."".

William Hunter (1748)

William Hunter (1718 – 1783)

Benedek *et al*, 2006, Osteoarthritis and Cartilage

Articular cartilage development

- Process of endochondral ossification
- Cells derived from mesenchyme during embryogenesis – cellular condensation prior to formation
- Lineage tracing studies implicate the GDF-5 cells are prominent in this process (Decker *et al*, 2017)

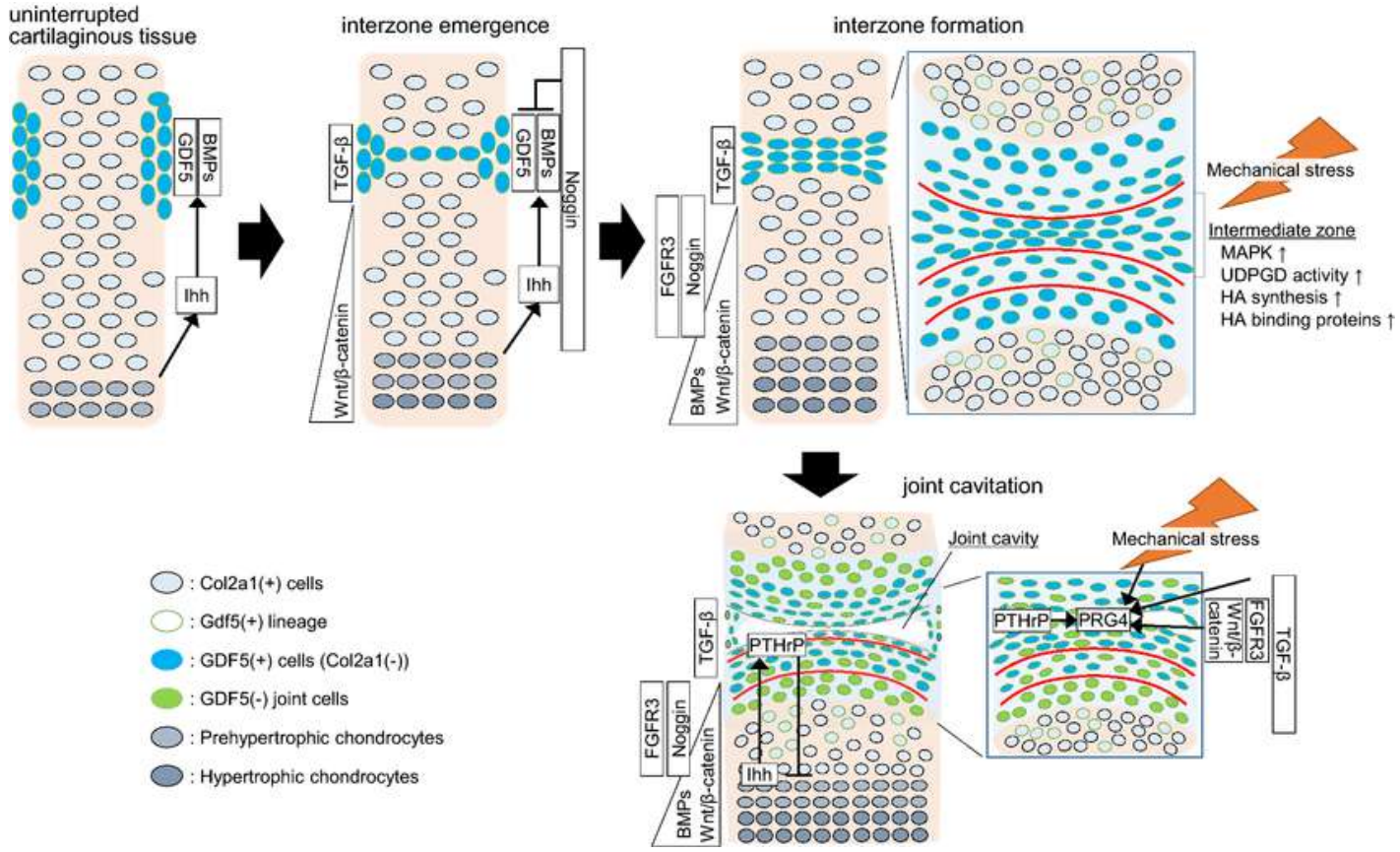
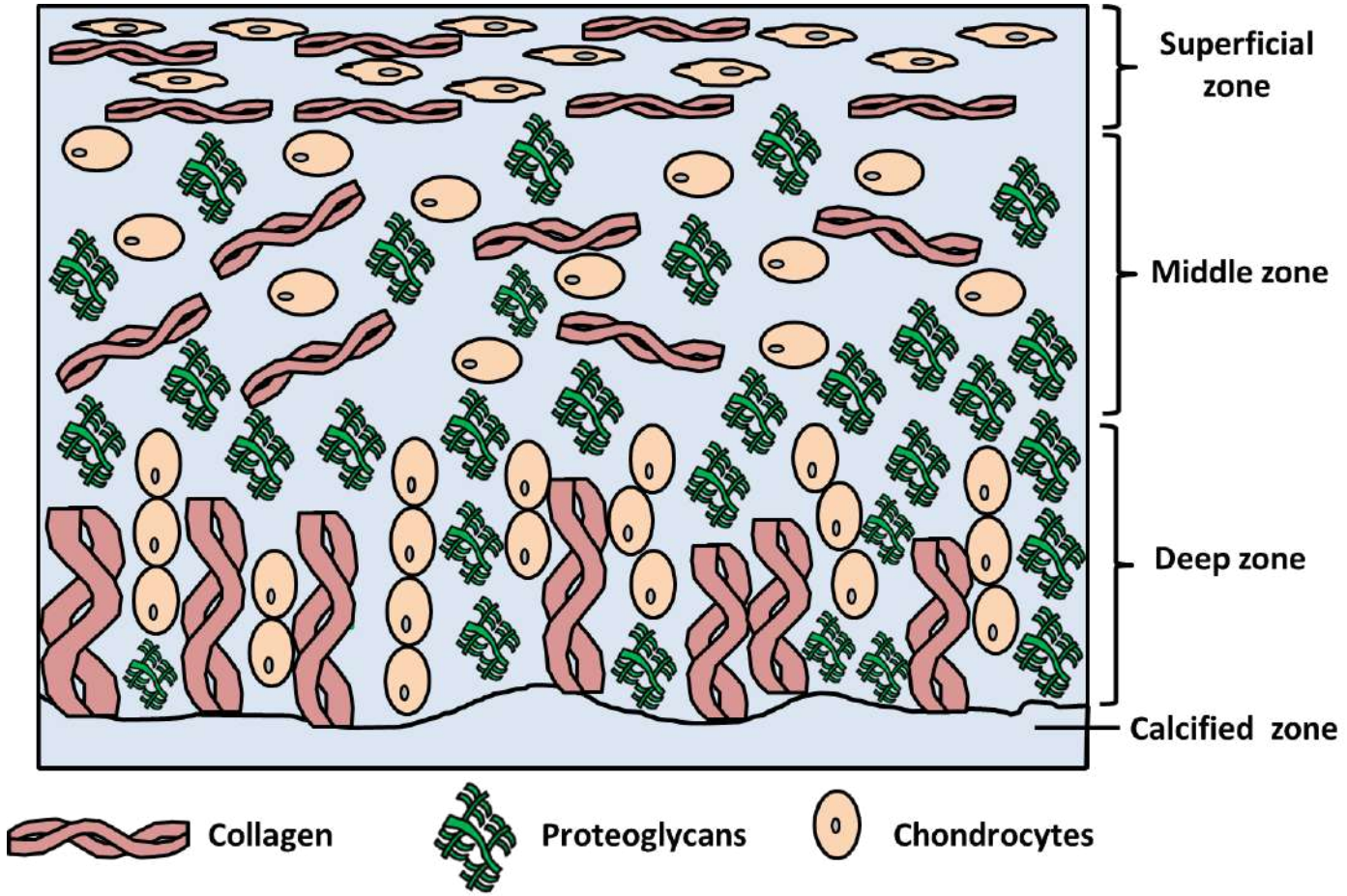


Image taken from Chijimatsu *et al*, 2019, Cell Mol Life Sci.

Structure of articular cartilage

- Heterogeneous structure
- Composition
  - Collagen II
  - Aggrecan and GAGs
  - Chondrocytes
  - Proteins (e.g. lubricin (PRG-4))
- Nerves and blood vessels found in the subchondral bone



Pericellular matrix of chondrocytes

- Immediate region around the chondrocyte
- Presence of small proteoglycans (e.g decorin) and other proteins (i.e. Matrillis, Cartilage Oligomatrix Protein (COMP))
- Purpose of pericullular matrix is in chondrocyte homeostasis and mechanical signalling

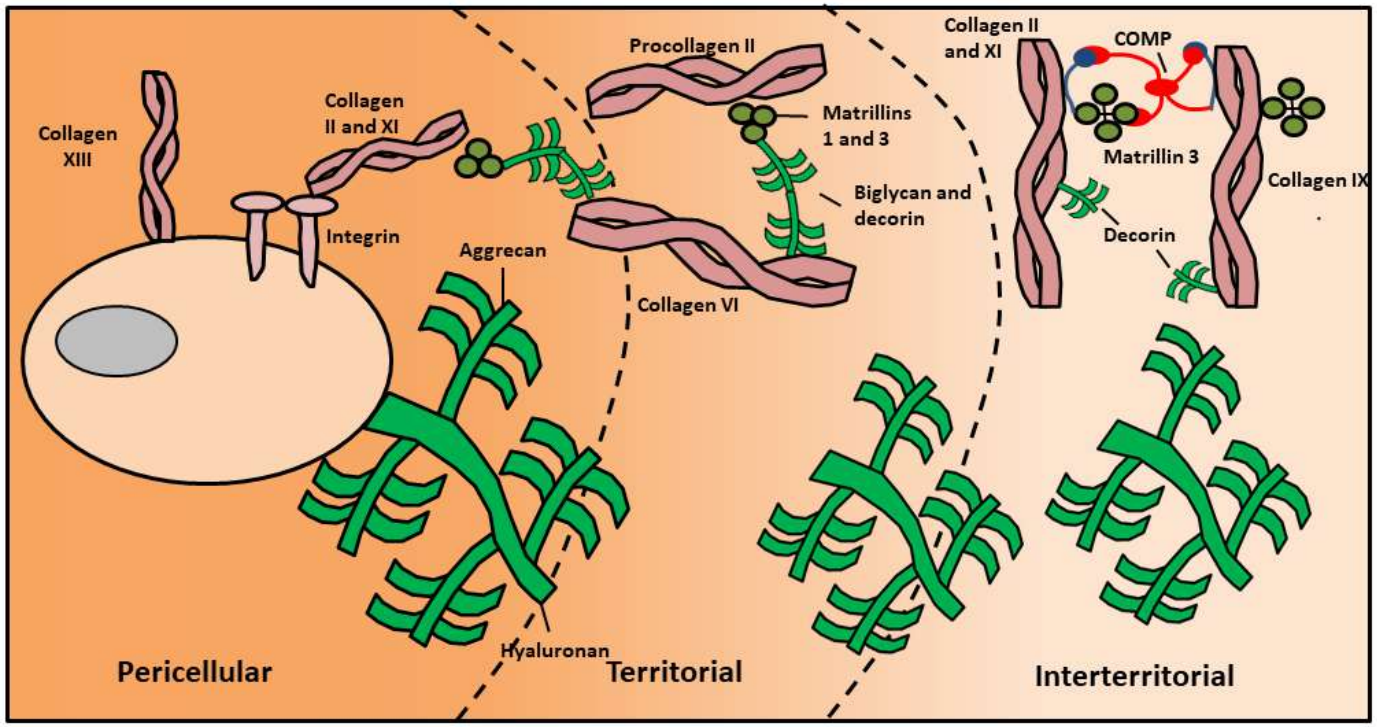


Image taken from Pattappa *et al*, 2019, eCM journal

Function of articular cartilage

- Joint lubrication

- Facilitate biomechanical loading during movement
  - Loading modalities
    - Hydrostatic pressure
    - Compression
    - Shear (fluid)

- Resist high contact forces in the underlying subchondral bone

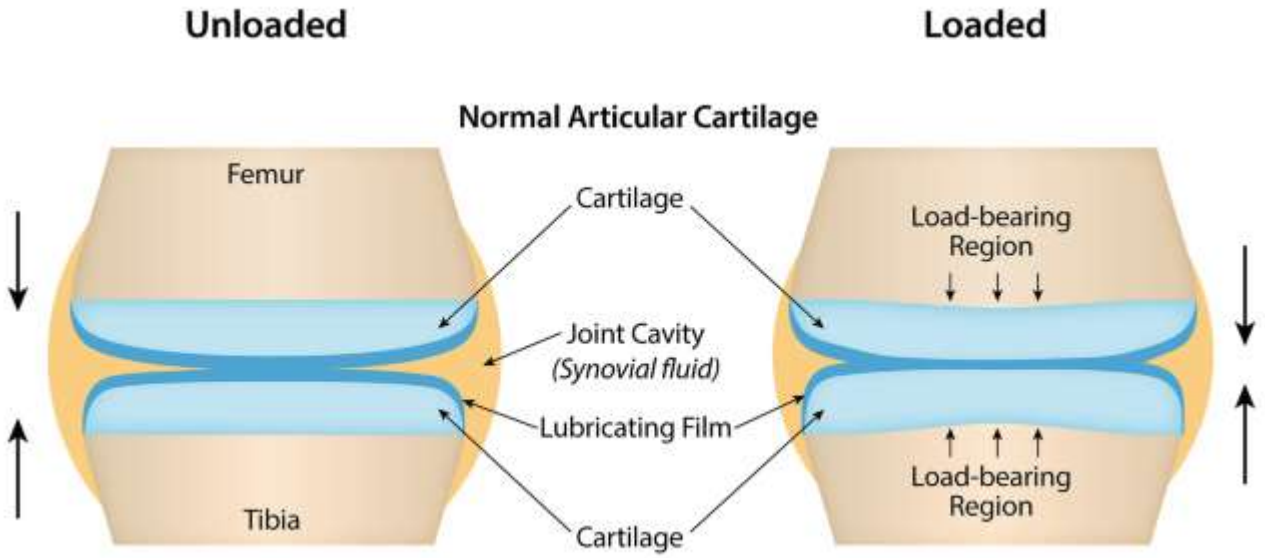


Image taken from Articular Cartilage of the Knee, 2020

GAGs helps cartilage resist compressive loads

- GAGs are negatively charged molecules that attract positive ions via water to induce an osmotic pressure for retaining water within the collagen network
- During loading, compression induces fluid flow (shear) and hydrostatic pressure releasing water
- Upon unloading, water re-enters and restore shape – viscoelastic properties of articular cartilage
- Thicker collagen fibres and more GAGs present in deep zone to resistance the compressive loading

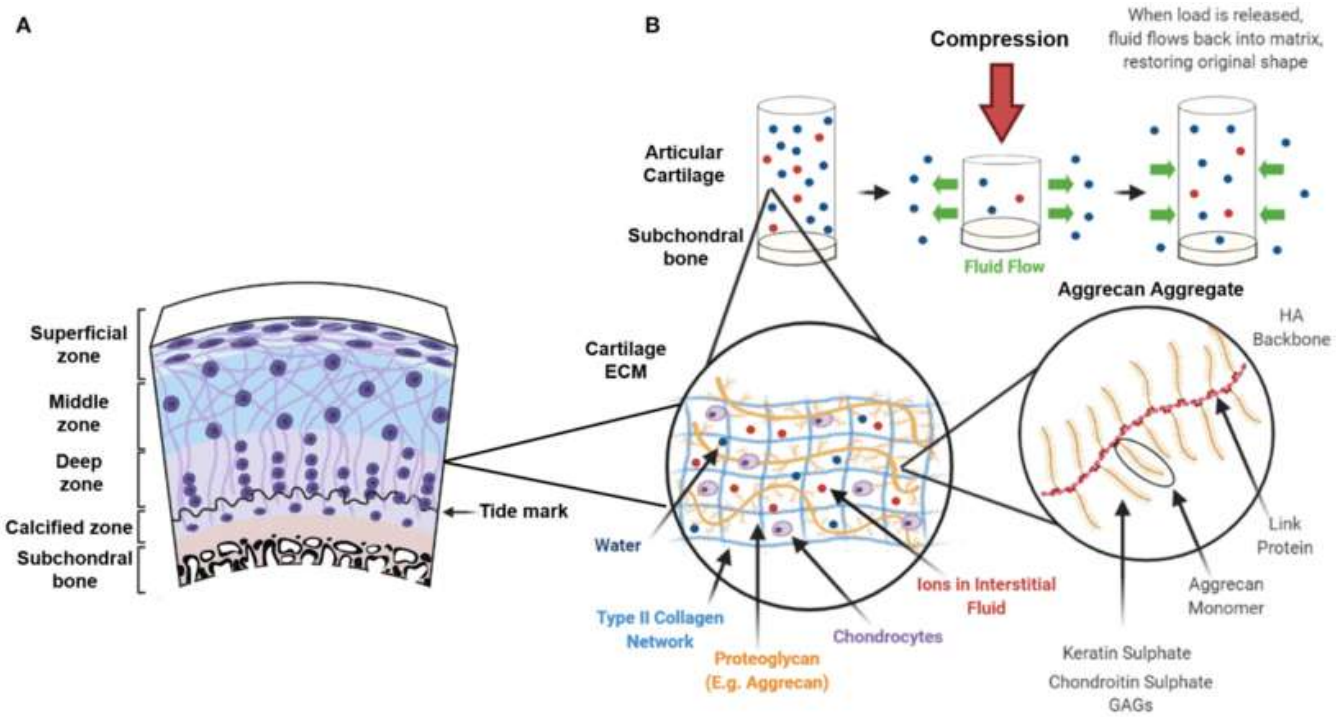


Image taken from Davis *et al*, 2021 Frontiers BioEngineering

Lubricin enables smooth joint movement

- Found in the superficial layer of cartilage
- Secreted by superficial zone chonodrocytes and synoviocytes (from the synovium)
- Helps in the gliding motion of cartilage to ensure frictionless movement

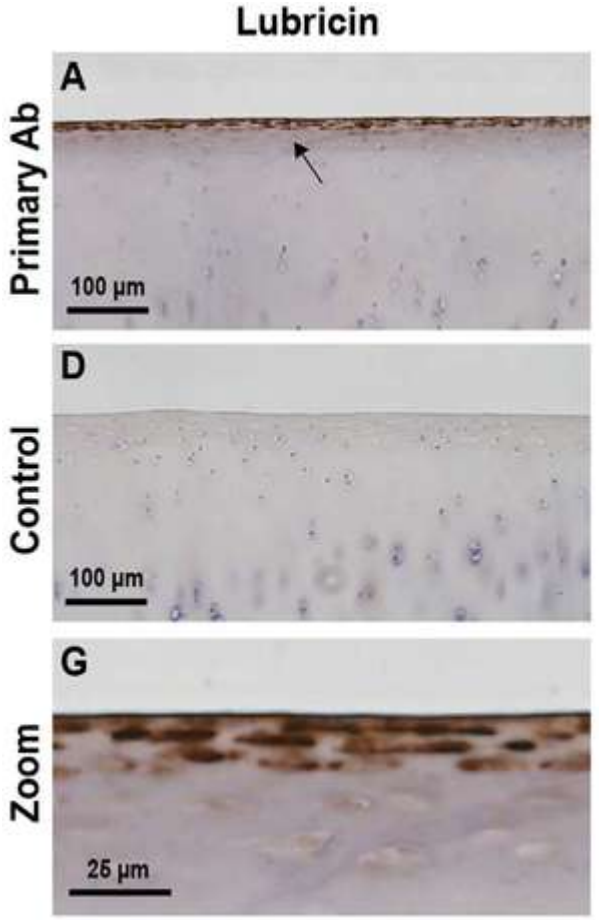
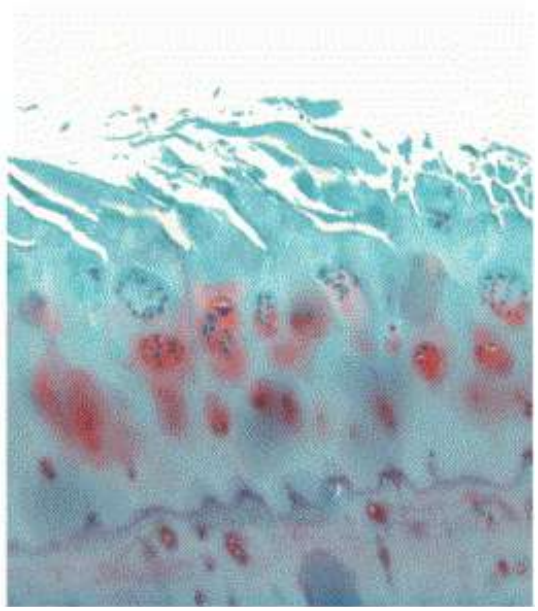
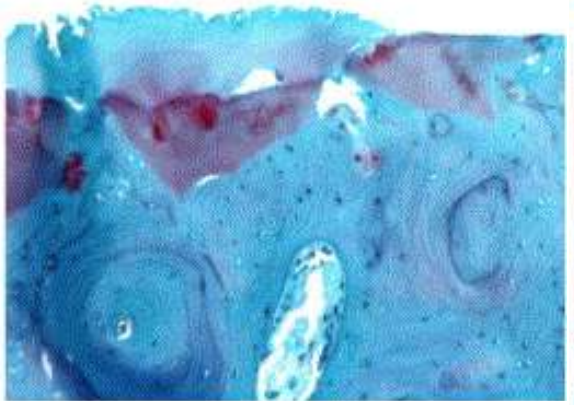


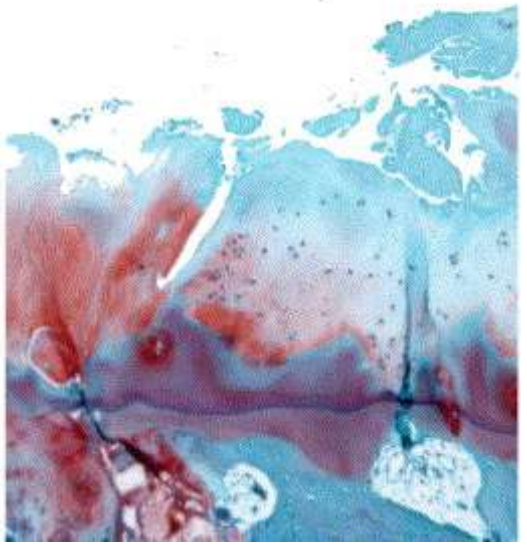
Image taken from Reesink *et al*, 2016, Scientific Reports

How do we get to this…..

Osteoarthritis (OA)







Healthy tissue

Grade 4

Grade 5

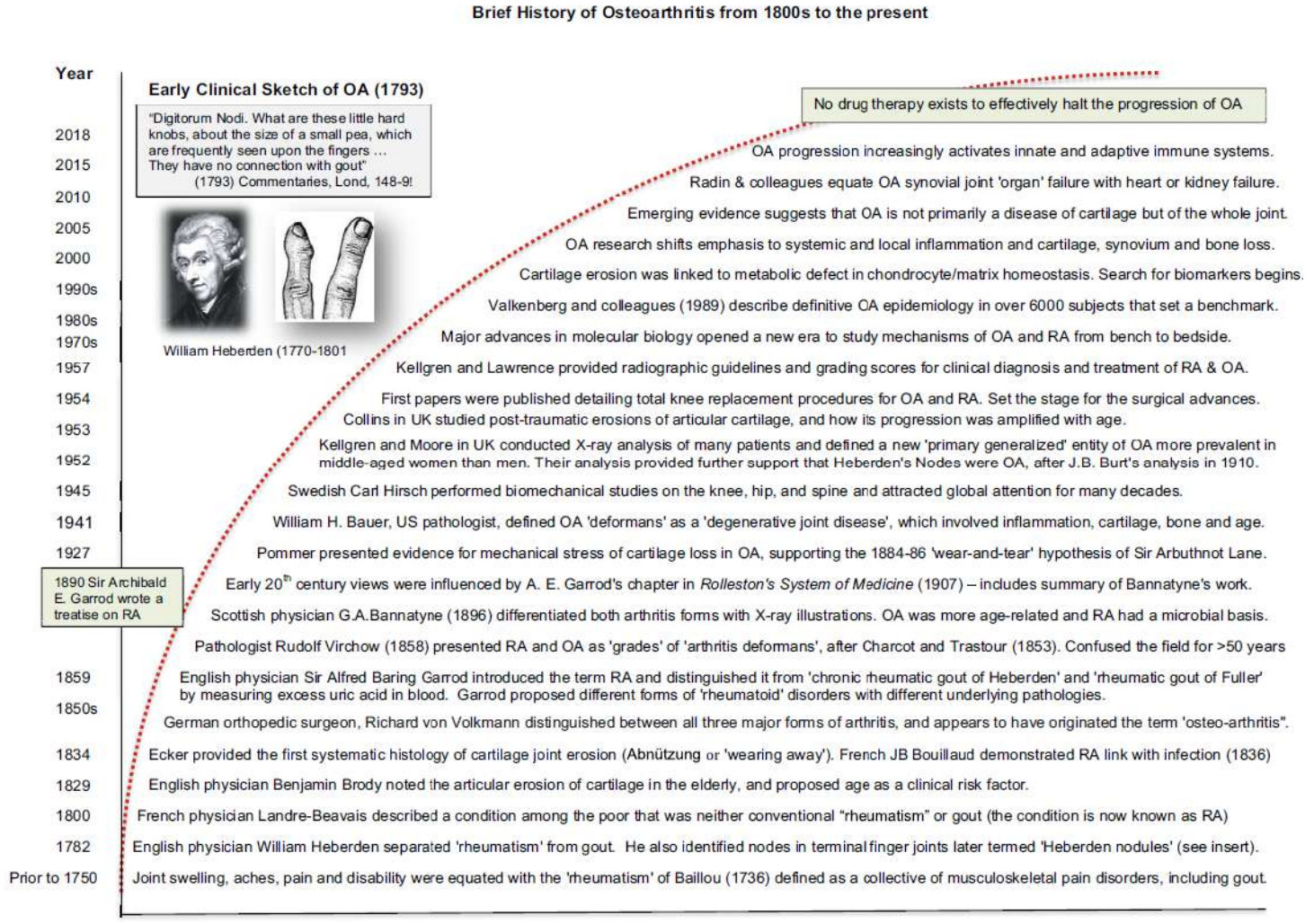
Grade 6

Osteoarthritis grade

Image taken from Pritzker *et al*, 2006, Osteoarthritis & Cartilage

Historical evolution of osteoarthritis (OA)

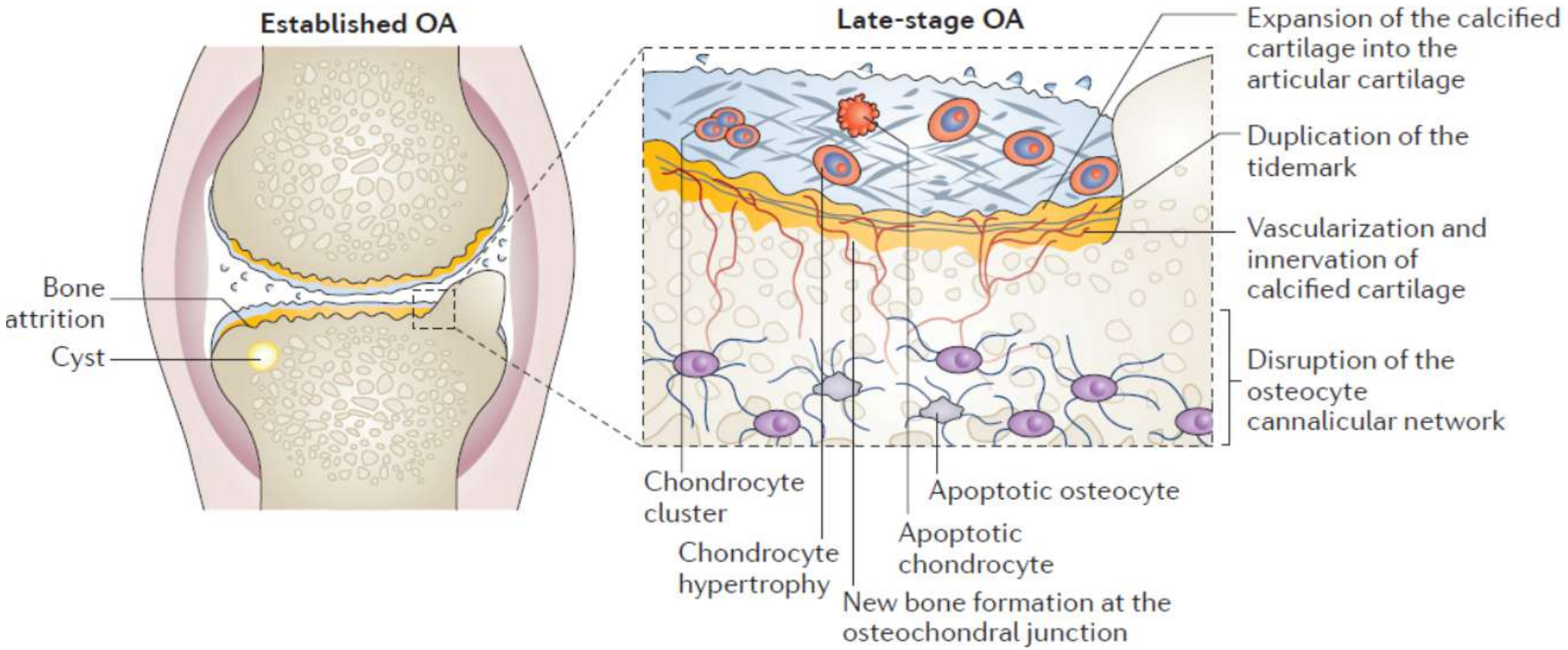
- OA has been known since late 18th century
- Definition of the disease has evolved with time
- Now termed a whole joint diease NOT solely cartilage



Dobson *et al*, 2018, Osteoarthritis & Cartilage

Biological etiology of OA

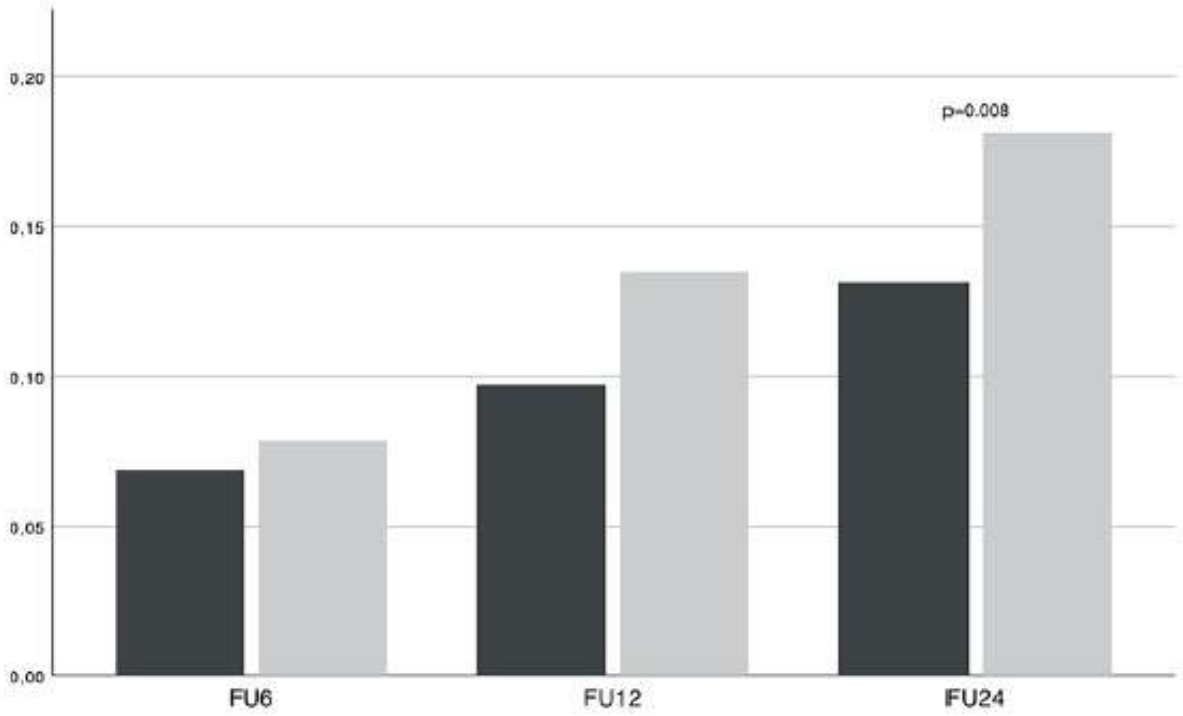
Late stage OA



Goldring et al, 2016, Nature Review Rheumatology.

Treating cartilage lesions using cell-based therapies

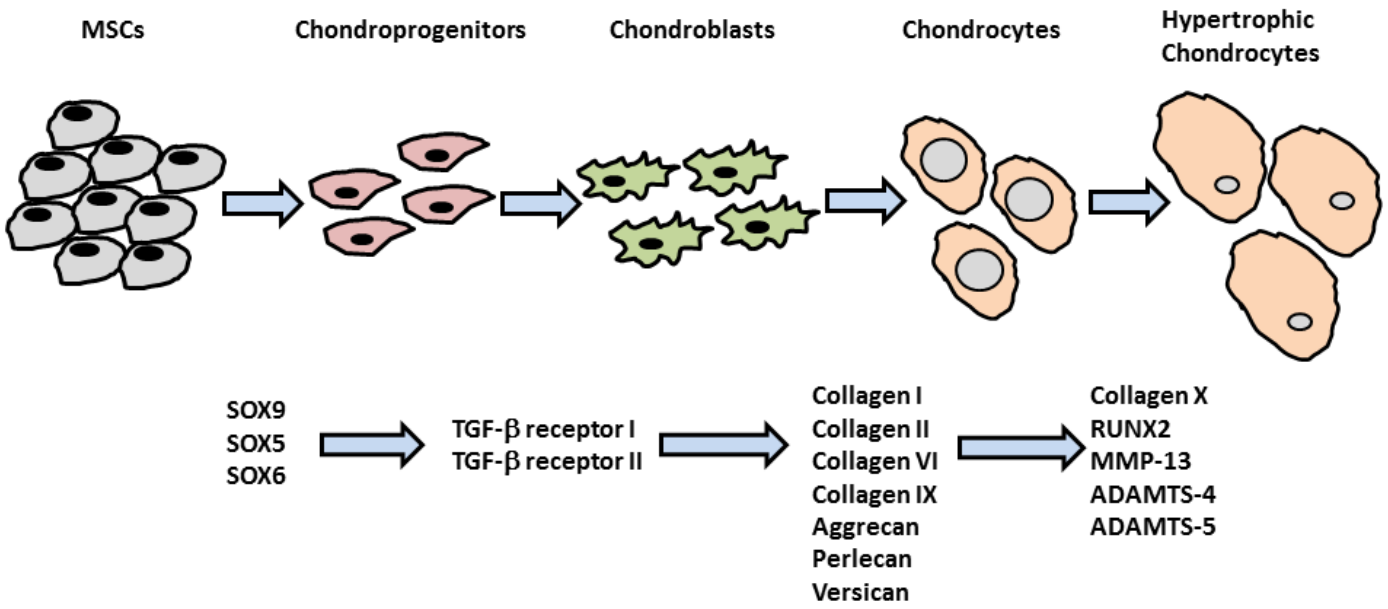
- Focal OA lesions are treatable using cell-based therapies
- Cell-based therapies for cartilage restoration include Autologous Chondrocyte Implantation (ACI) and Matrix Assisted Chondrocyte Transplantation (MACT)
- However, there are high re-operation rates for degenerative lesions and in female population



Data from Faber *et al*, 2022 Cartilage

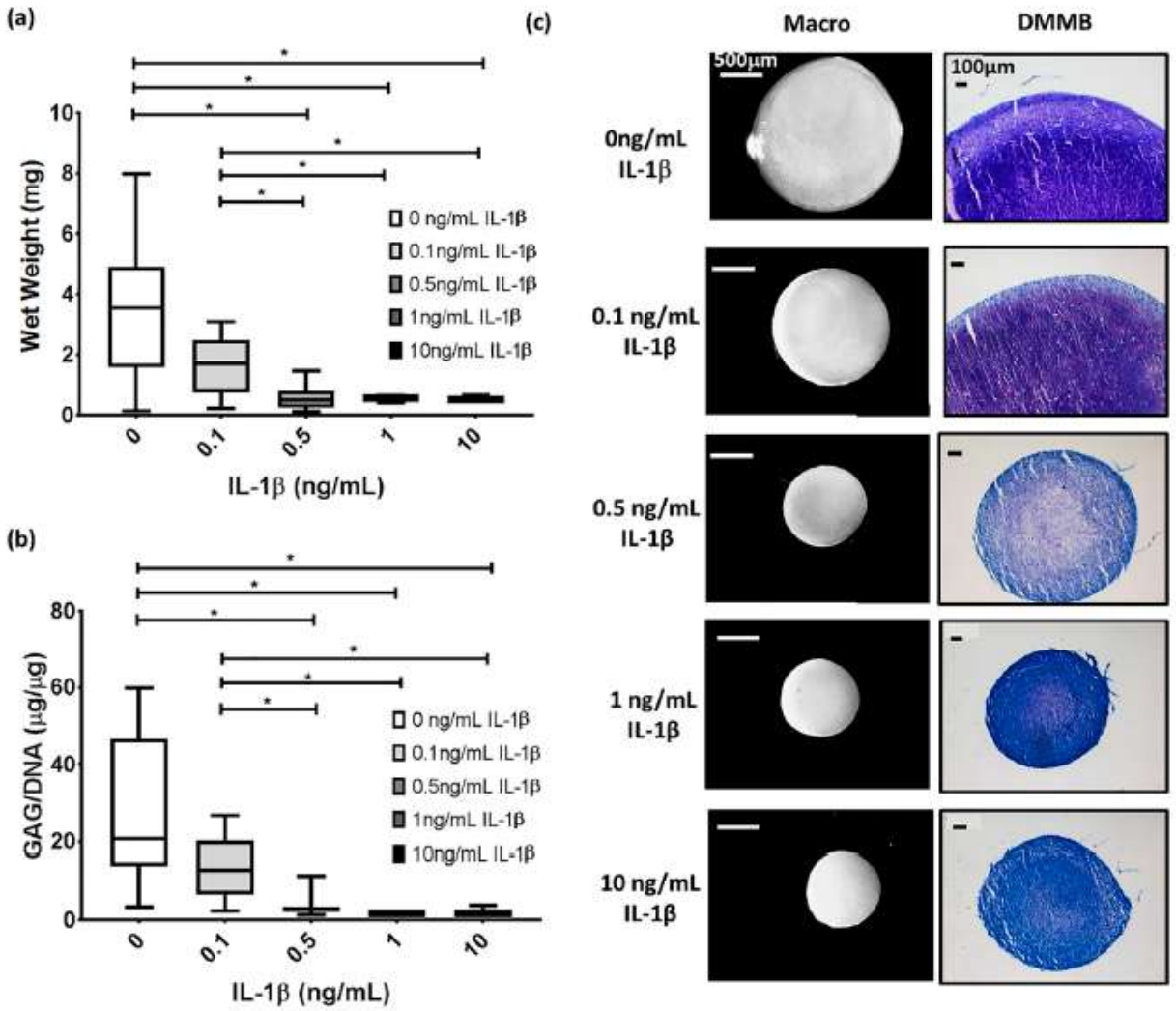
Alternative cell type: Mesenchymal stromal cells (MSCs)

- Mesenchymal stromal cells (MSCs) derived from a variety of sources , primarily bone marrow, adipose or synovium for cartilage
- Process for developing cartilage recapitulates embryological cartilage formation (Johnstone *et al*, 1998)
- Presence of growth factors are a primary requirement, e.g. TGF-β



Inflammatory cytokines

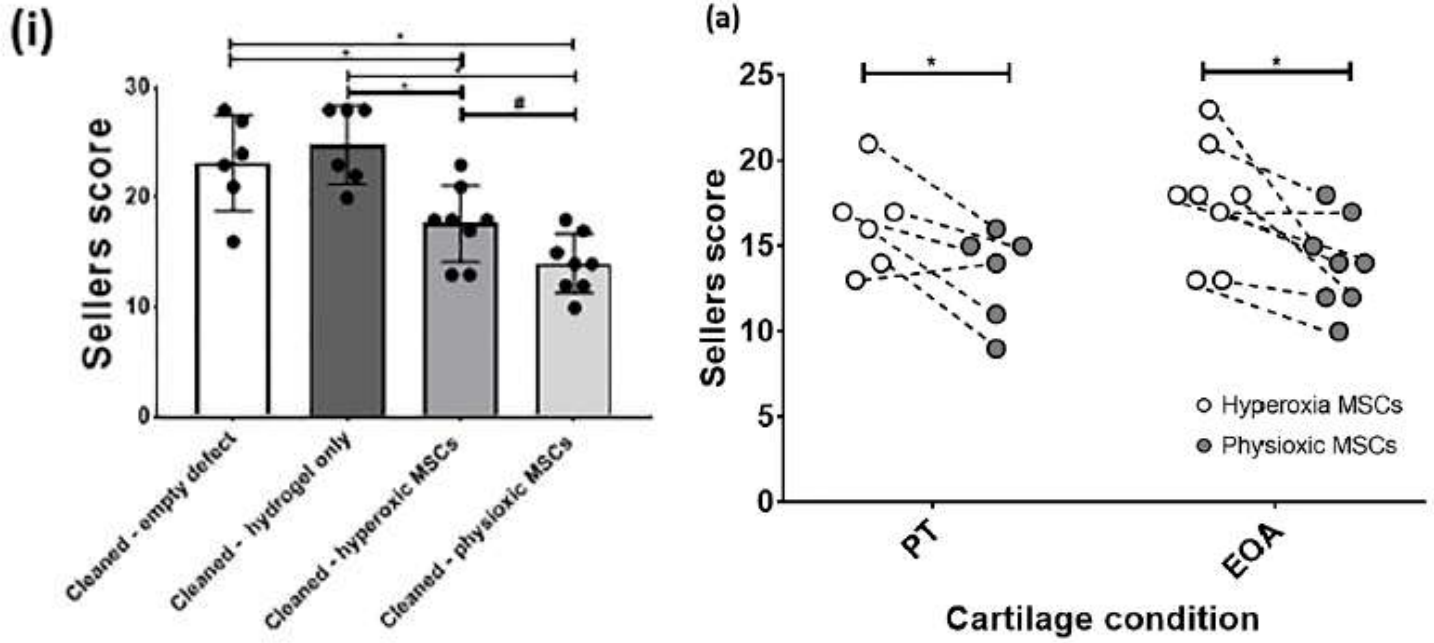
- Presence of inflammatory cytokines increases OA progression
- Stimulates matrix degradation via ADAMTS-5 and MMP-13
- Elevated IL-1β presence in OA chondrocytes
- MACT implants from early OA lesions upregulates IL-1β
- How can we counter IL-1β inhibition ?



Pattappa *et al*, Cells, 2019

Physioxia counters IL-1β inhibited chondrogenesis

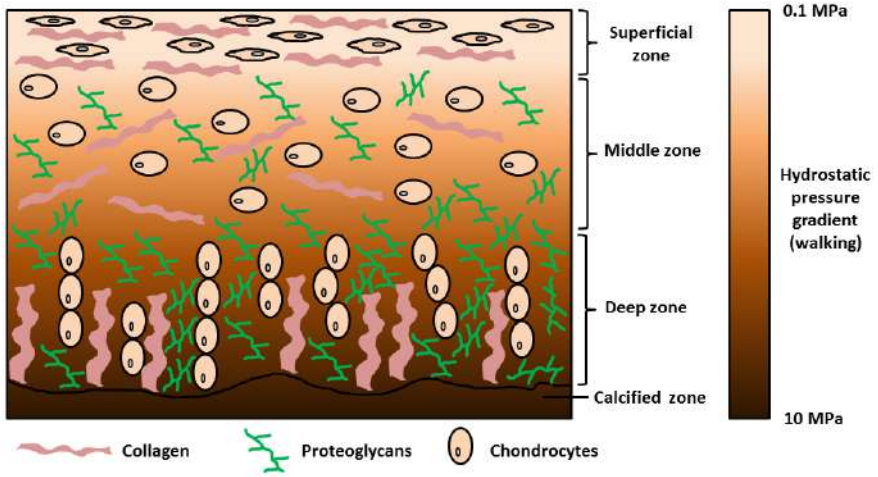
- Cells within the knee joint are under a low oxygen tension (2-5%) or physioxia (Lafont *et al*, 2010)
- Beneficial effect on chondrocytes and chondrogenic MSCs – in vitro (reviewed Pattappa *et al*, 2019)
- Physioxia counters IL-1β inhibited MSC chondrogenesis *in vitro*
- Improvement in cartilage regeneration with physioxia preconditioned MSCs in an early OA model



Pattappa *et al*, 2020, Biology

Mechanobiology can help produce stable cartilage

- Cartilage loaded under compression and shear
- Compression and shear loading helps to increase and induce appearance of stable neo articular cartilage
- Hydrostatic pressure (part of above – fluid pressurization) also contributes to process – timing of load is important
- NOTE: Environmental stimuli has a donor dependent response



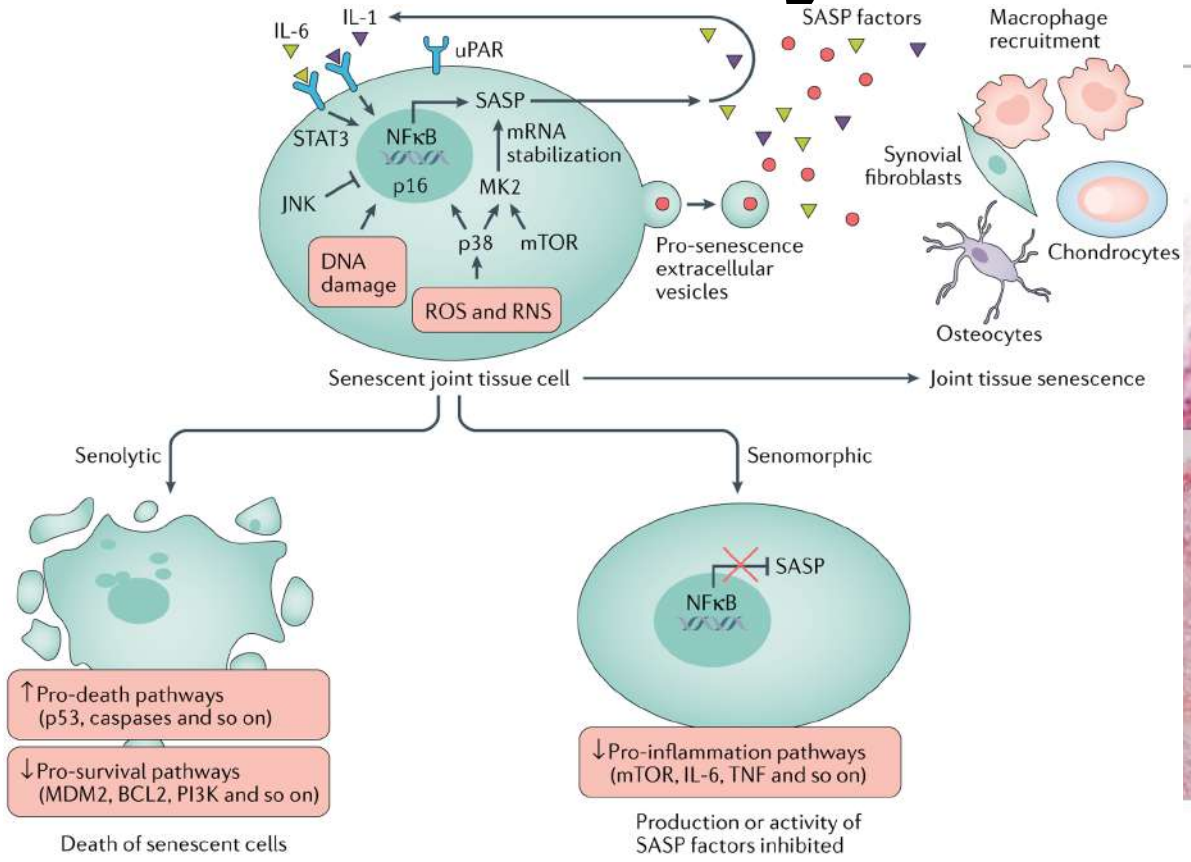
Pattappa *et al*, 2018, ecM journal

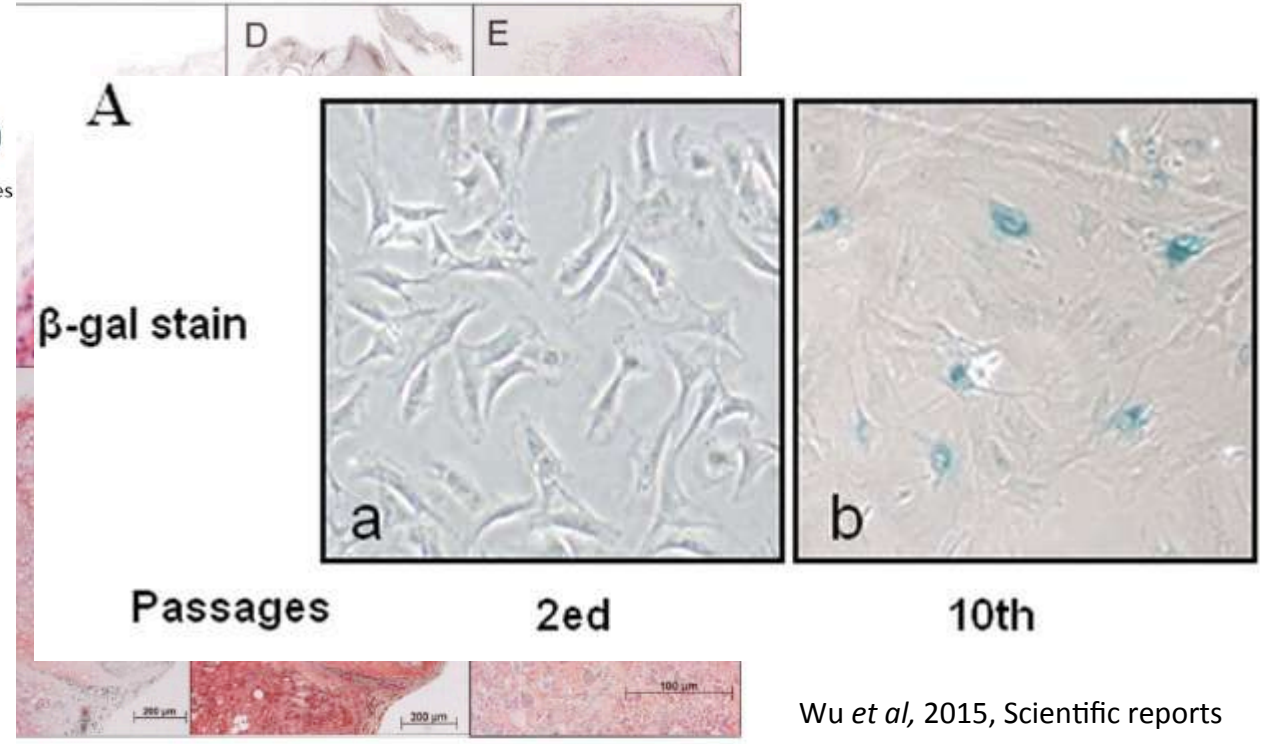
Unloaded

Week 1 loaded

Angele *et al,* 2003, JOR

MSCs induce bone formation in vivo and chondrocytes undergo senescence





Wu *et al,* 2015, Scientific reports

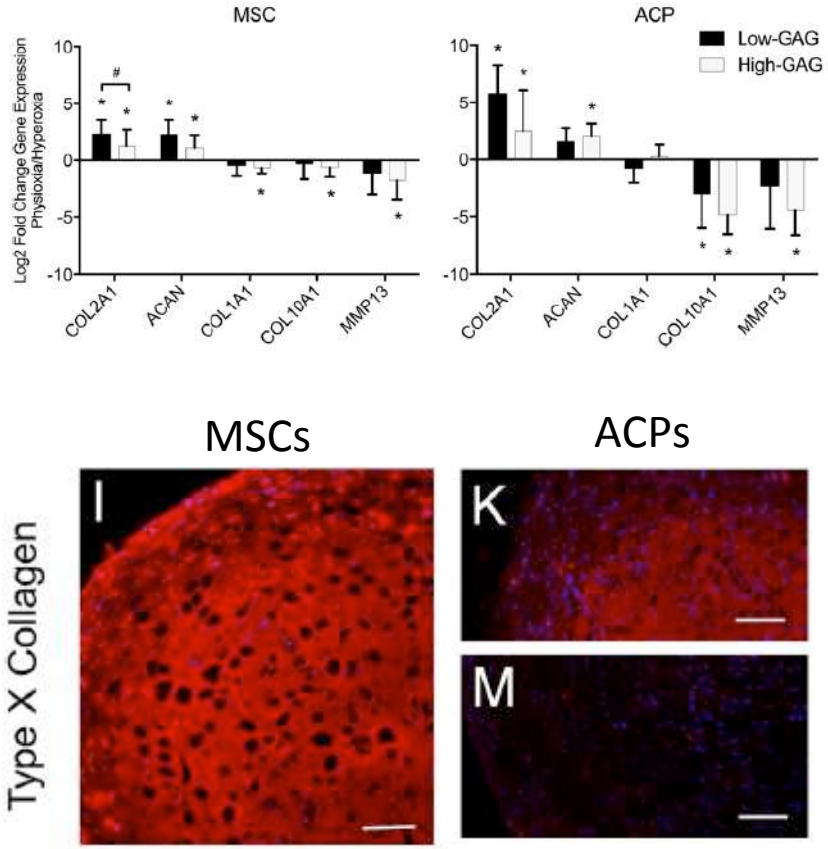
Pelttari *et al,* 2006, Arthritis and Rheumantism

Coryell *et al,* 2020, Nat. Rev. Rheumatology

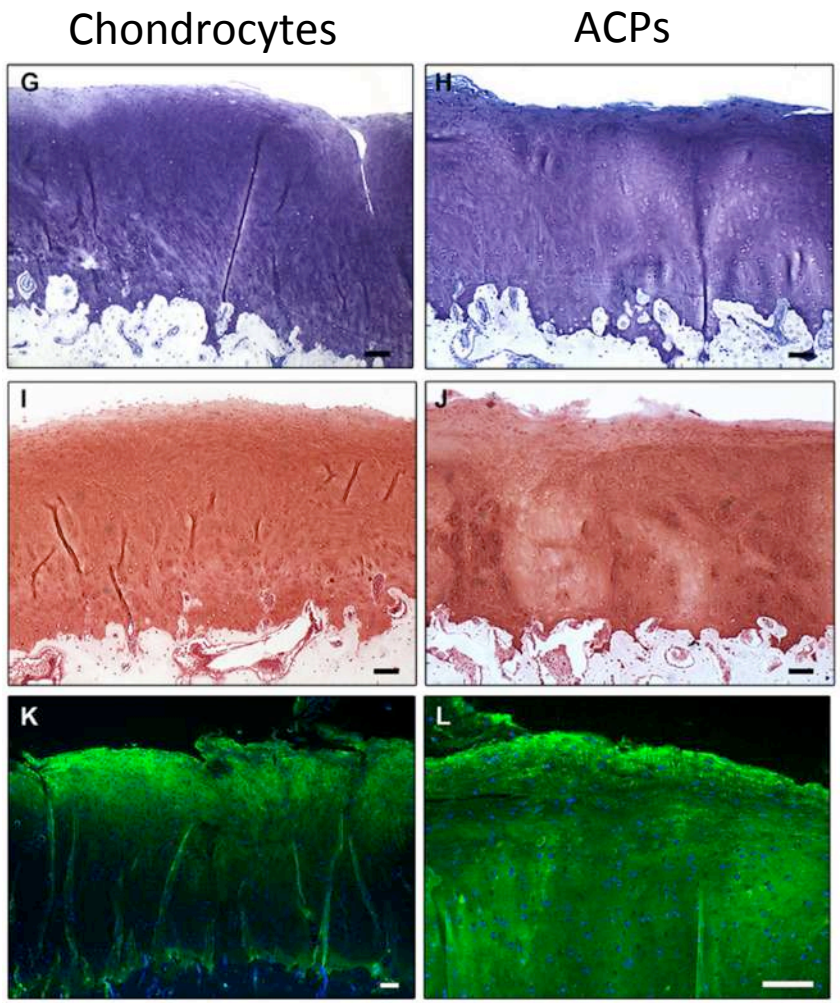
- Both phenomena can be partially countered by environmental stimuli, e.g. physioxia
- Are there other ways to reduce this or is there another cell type that can be used ?

Articular cartilage progenitors (ACPs)

- Found on surface of articular cartilage – both healthy and OA cartilage
- Adherence by fibroenectin for *in vitro* expansion – telomerase positive
- No hypertophic differentiation
- Stable cartilage *in vivo*
- Clinical studies required



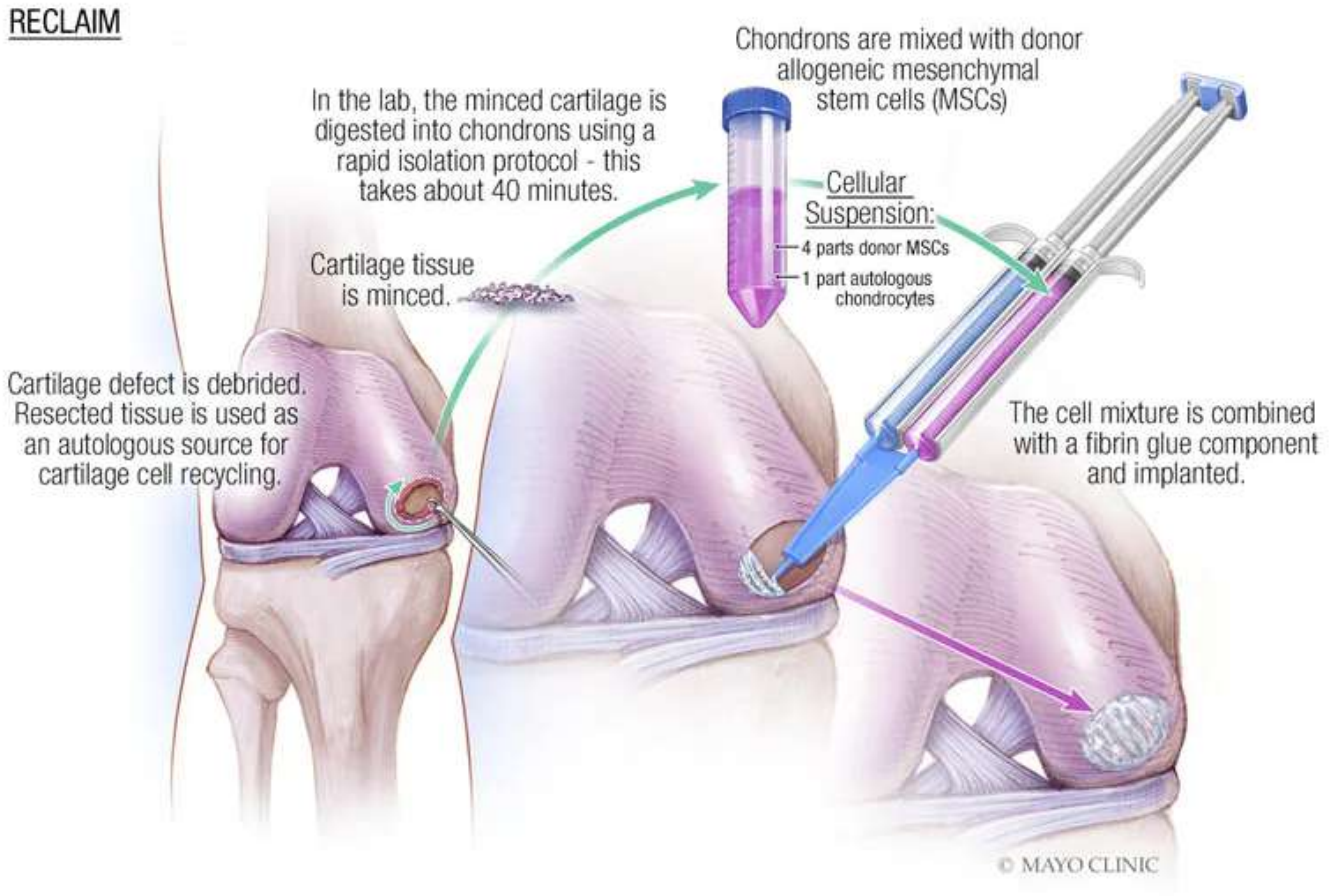
Anderson *et al*, 2010, Stem Cell Research & Therapy



Williams *et al*, 2010, PLoS One

Chondrons

- One-step procedure
- Partially digested minced cartilage isolates chondrocytes surrounded by their pericellular matrix – chondron
- Co-cultured with MSCs – increase cartilage matrix production (Bekkers *et al*, 2013)
- Implanted combined with fibrin glue
- Clinical results show positive outcomes with stable cartilage (de Windt *et al*, 2017; Korpershoek *et al*, 2020)



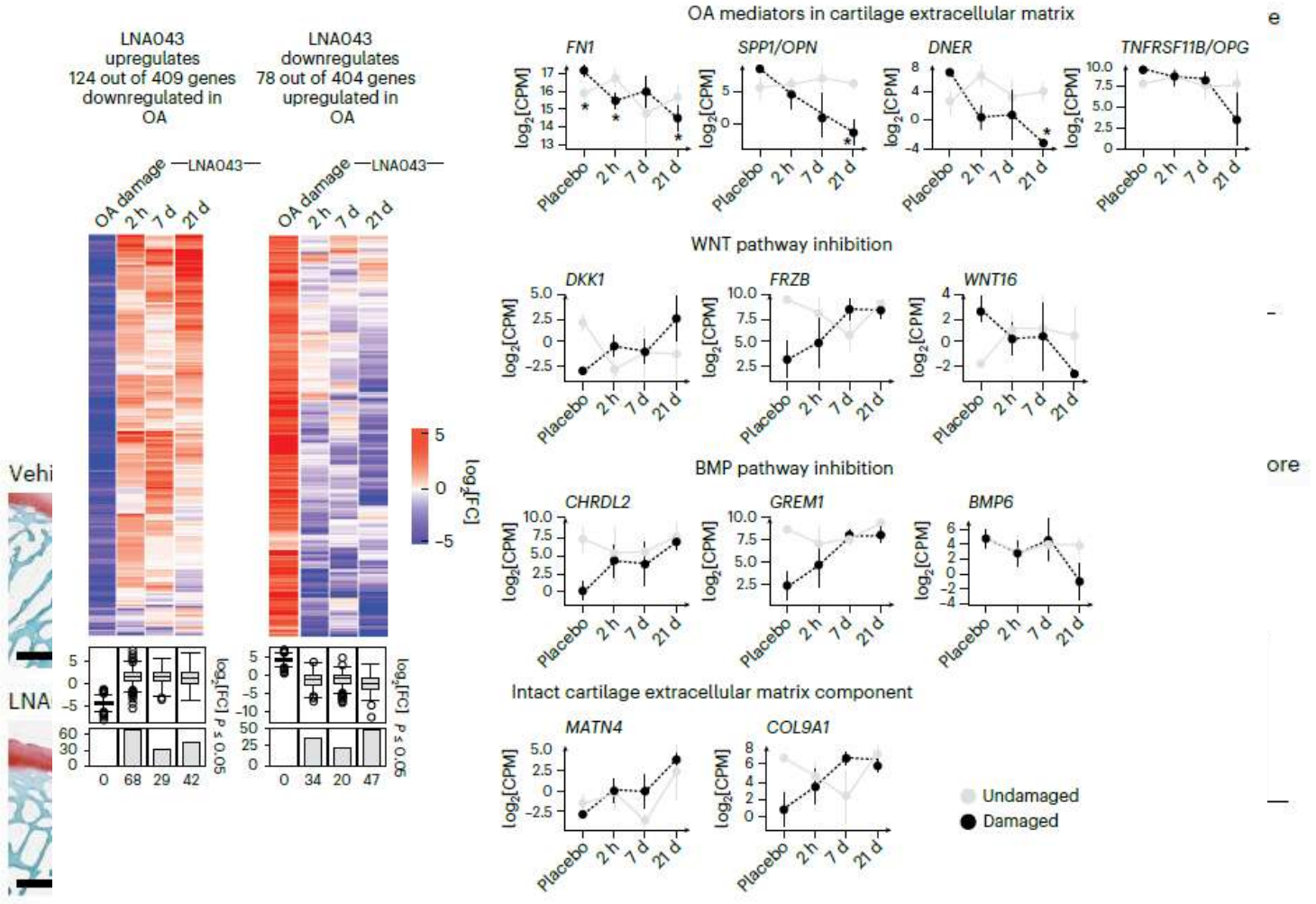
The future: Pharmacological drugs

Type of drug	Drug name	Route of administration	Current phase of development	ClinicalTrials.gov identifier
Wnt inhibitor	Lorecivivint (small molecule)	Intra-articular	Phase III (knee OA)	NCT03928184
NGF inhibitor	Tanezumab (neutralizing antibody)	Subcutaneous	Phase III (hip or knee OA)	NCT02528188
	Fasinumab (neutralizing antibody)		Phase III (hip or knee OA)	NCT02683239, NCT03161093, NCT03304379
TrkA inhibitor	ASP7962 (small molecule)	Oral	Phase II (knee OA)	NCT02611466
	GZ389988A (small molecule)	Intra-articular	Phase II (knee OA)	NCT02845271
TRPV1 modulator	CNTX-4875 (trans-capsaicin)	Intra-articular	Phase III (knee OA)	NCT03660943, NCT03661996
	NEO6860	Oral	Phase II (knee OA)	NCT02712957
rhFGF18	Sprifermin	Intra-articular	Phase II (knee OA)	NCT01919164
ADAMTS5 inhibitor	GLPG1972/S201086 (small molecule)	Oral	Phase II (knee OA)	NCT03595618
	M6495 (neutralizing antibody)	Subcutaneous	Phase I (knee OA)	NCT03583346
Senolytic drug	UBX0101	Intra-articular	Phase II (knee OA)	NCT04129944, NCT04229225
	Fisetin	Oral	Phase I–II (knee OA)	NCT04210986
Cathepsin K inhibitor	MIV-711 (small molecule)	Oral	Phase II (knee OA)	NCT02705625, NCT03037489
IL-6R inhibitor	Tocilizumab (neutralizing antibody)	Intravenous	Phase III (hand OA)	NCT02477059
CCL17 inhibitor	GSK3858279 (neutralizing antibody)	Intravenous, subcutaneous	Phase I (knee OA)	NCT03485365
GM-CSF inhibitor	Otilimab (neutralizing antibody)	Subcutaneous	Phase II (hand OA)	NCT02683785
Promoter of endogenous progenitor cell differentiation	KA34	Intra-articular	Phase I (knee OA)	NCT03133676
Gene therapy	TissueGene-C (allogeneic chondrocytes expressing TGFβ1)	Intra-articular	Phase III (knee OA)	NCT03203330, NCT03291470
	ART-I02 (AAV-5 vector encoding human IFNβ)	Intra-articular	Phase I (hand OA)	NCT02727764
	FX201 (AAV carrying IL-1Ra cDNA)	Intra-articular	Phase I (knee OA)	NCT04119687
	sc-rAAV2.5IL-1Ra (AAV carrying IL-1Ra cDNA)	Intra-articular	Phase I (knee OA)	NCT02790723
	XT-150 (DNA plasmid with *IL10* transgene)	Intra-articular	Phase II (knee OA)	NCT04124042

Latourte *et al*, 2022, Nature Review Rheumatology

Newest OA therapeutic: Angiopoeitin-like-3-derivative (LNA043)

- LNA043 uncovered from phenotypic screen
  - Induced under physioxia (Mathieu *et al*, Journal of Biological Chemistry, 2014)
  - Binds to fibronectin receptor, $\alpha_5\beta_1$ integrin (Perez-Garcia *et al*, Cells, 2019)
- LNA043 injection significantly improved cartilage regeneration in a mini-pig model
- Phase 1 clinical trial demonstrates a change in the transcriptome of OA patients towards a regenerative state



Gerwin *et al*, 2022, Nature Medicine

Summary

- Articular cartilage has a heterogeneous structure with viscoelastic properties to support its biomechanical function
- Inflammatory cytokines and changes in joint loading result in OA
- A variety of therapies based on understanding cartilage structure and function have been developed to treat OA

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