Osteoarthritis is a global disease with pathological changes occurring in all the joint tissues. What is the relative contribution at different stages? How do the tissues interact?

Transcriptome-wide analysis of messenger RNA decay in normal and osteoarthritic human articular chondrocytes.

Findings:
• Majority of chondrocyte-expressed transcripts were stable, but a subset exhibited a rapid decay
• Strong bias toward shortening of mRNA half-life in OA chondrocytes.
• Among those short-lived transcripts: Genes involved in transcriptional regulation & the regulation of programmed cell death.
• First transcriptome-wide study on mRNA decay in cartilage – adds to our understanding of gene expression in OA
A homeostatic function of CXCR2 signalling in articular cartilage.

This study uncovered an unexpected homeostatic role for CXCR2 signaling in articular cartilage:

- CXCL6 was present in territorial matrix of healthy human cartilage, but not in early OA
- Disruption in CXCR2 signaling resulted in:
  A) *In vitro*: decreased ECM production
  B) *In vivo*: increased susceptibility to OA after DMM

**Significance:**
- Suggests that the loss of CXCL6 during cartilage breakdown contributes to the loss of chondrocyte phenotypic stability.
Regulation of the catabolic cascade in osteoarthritis by the zinc-ZIP8-MTF1 axis.
(Commentary by V. Byers Kraus, in News and Views, Nature March 2014)

Novel pathway that promotes the pro-catabolic phenotype

Chondrocyte-specific Zip8 overexpression in mice (Col2a1 promoter).
By 12 months: accelerated cartilage damage + SCB sclerosis in the absence of overt synovitis.

Substantiates the idea that cartilage damage can drive changes in other joint tissues (SCB)

Local interference with the zinc cascade may provide a therapeutic approach for OA
**Damaged cartilage as a source of DAMPs**

Bioactivity in an aggrecan 32mer fragment is mediated via Toll-like receptor 2.

**Aim:** To determine whether an aggrecan 32-mer fragment derived from dual ADAMTS and MMP cleavage in the aggrecan interglobular domain is bioactive.

**Results:**

- 32-mer had anti-anabolic, pro-catabolic and pro-inflammatory bioactivity *in vitro* on chondrocytes, synovial fibroblasts, and macrophages.
- The effect is mediated through TLR2.

**Significance:**

- First demonstration of a TLR ligand derived from one of the major cartilage macromolecules.
- In vivo?
Osteoarthritis is a global disease with pathological changes occurring in all the joint tissues. What is the relative contribution at different stages? How do the tissues interact?
Histopathological features associated with symptomatic knee OA:
1. Synovitis
2. Synovial area positive for NGF staining
Chondrocytes/cartilage as a source of Nerve Growth Factor (NGF). Which stimuli induce it?

1. Induction of nerve growth factor expression and release by mechanical and inflammatory stimuli in chondrocytes: possible involvement in osteoarthritis pain.
   Arthritis Res Ther. 2014; 16 R16
   murine and human chondrocytes
   stimuli: IL-1β and visfatin

2. TGF-β is a potent inducer of Nerve Growth Factor in articular cartilage via the ALK5-Smad2/3 pathway. Potential role in OA related pain?
   Blaney Davidson EN, van Caam AP, Vitters EL, Bennink MB, Thijsse E, van den Berg WB, Koenders MI, van Lent PL, van de Loo FA, van der Kraan PM.
   Osteoarthritis Cartilage. 2015 Mar;23(3):478-86.
   bovine and human chondrocytes/explants
   TGFβ1 is a potent inducer of NGF mRNA, in a ALK5/Smad2/3-dependent manner

Long-term analgesic effect of a single dose of anti-NGF antibody on pain during motion without notable suppression of joint edema and lesion in a rat model of osteoarthritis.
   Ishikawa G, Koya Y, Tanaka H, Nagakura Y.

A single dose of anti-NGF antibody exerts a long-lasting analgesic effect on pain during motion (gait) in a rat MIA model (day 3-Day 35); no effect on edema or macroscopic lesions
Synovium and Disease progression

Treatment efficacy of adipose-derived stem cells in experimental osteoarthritis is driven by high synovial activation and reflected by S100A8/A9 serum levels.

Findings:
- IA adipose-derived stem cells were efficacious in a model with high synovial activation (collagenase-induced) but not in a model with low levels of synovitis (DMM).
- Efficacy was associated with suppression of synovial activation and suppression of S100A8 & S100A9 in joint and in serum.

Dispensable role of myeloid differentiation primary response gene 88 (MyD88) and MyD88-dependent toll-like receptors (TLRs) in a murine model of osteoarthritis.
Nasi S, Ea HK, Chobaz V, van Lent P, Lioté F, So A, Busso N.

Findings: TLR-1, TLR-2, TLR-4, TLR6, or MyD88 ko mice were not protected in a surgically induced OA model (MNX-females).

Significance: Alarmins/TLRs may contribute to driving OA progression in subsets with high degree of inflammation/synovitis. This may have therapeutic implications.

Findings:

• PAR-2 ablation had a chondroprotective effect in DMM model (8 weeks)

• The primary protective effects of PAR2 ablation occur via modulation of subchondral bone remodeling and synovial macrophage activation

Significance:

• There is synovitis in the DMM model, and it may contribute to driving disease.
Osteoarthritis is a global disease with pathological changes occurring in all the joint tissues. What is the relative contribution at different stages? How do the tissues interact?

Subsets of Osteoarthritis can be driven by distinct risk factors, e.g., obesity, age, PTOA. Specific disease mechanisms?

Increased focus on mechanisms that link obesity and OA
Not just mechanical factors related to weight
But focus on inflammatory and metabolic factors associated with obesity.

Life-long caloric restriction does not alter the severity of age-related osteoarthritis.
McNeill JN, Wu CL, Rabey KN, Schmitt D, Guilak F.
Age (Dordr). 2014;36(4):9669

C57BL/NIA mice were fed either a calorie-restricted (CR) or an ad libitum (AL) diet (14 weeks- 24 months).

**Findings:**
- Although AL mice were heavier than CR mice, there was no difference in Mankin score or synovitis

**Significance:** Dietary composition may be important

Dietary fatty acid content regulates wound repair and the pathogenesis of osteoarthritis following joint injury.

The ratio of ω-6 to ω-3 polyunsaturated fatty acids (PUFAs) is considered one of the most important dietary mediators of inflammation.
Mice were fed a HFD – DMM at 16 weeks:
- HFD led to obesity
- But when enriched in ω-3 PUFAs, OA was much milder, with less synovitis
- SFA and ω6- PUFA independently acted as a detrimental factor in OA following DMM
- Injury-induced OA was associated with dietary content and serum levels of inflammatory adipokines but not with body weight

**Significance:** May provide a path toward clinical studies of dietary fatty acids supplements
Peroxisome proliferator-activated receptor δ promotes the progression of posttraumatic osteoarthritis in a mouse model.

• PPARs: a family of nuclear receptors activated by lipid ligands
• PPARδ activation promotes catabolic processes in chondrocytes & cartilage
• Cartilage-specific (Col II-cre) Ppard knockout mice were protected after DMM surgery (cartilage damage)
Aging and Osteoarthritis: Autophagy

The relationship of autophagy defects and cartilage damage during joint aging in a mouse model.
Caramés B, Olmer M, Kiosses WB, Lotz M.

Young (6 mo) Old (28mo) mouse

• In vivo analysis of basal autophagy activation in cartilage, using GFP-LC3 reporter mice
• Reduction in number of autophagic vesicles in chondrocytes with age
• This preceded cartilage damage

Significance: Suggests that autophagy decreases with age, which contributes to joint damage.

PPARγ deficiency results in severe, accelerated osteoarthritis associated with aberrant mTOR signalling in the articular cartilage.

• Inducible cartilage-specific PPARγ KO mice, subjected to DMM : accelerated cartilage degradation, chondrocyte apoptosis, with increased mTOR expression and suppression of autophagy markers.
• PPARγ-mTOR double KO rescued phenotype

Significance: PPARγ maintains articular cartilage homeostasis, partly through the mTOR pathway.
**In vitro studies on aging cartilage and chondrocyte senescence**

AMPK inhibits chondrocyte pro-catabolic responses
AMPK signaling decreases with age

**Peroxisome proliferator-activated receptor γ coactivator 1α and FoxO3A mediate chondroprotection by AMP-activated protein kinase.**

- The chondroprotective effect of AMPK is at least partly mediated by 2 major downstream targets, PGC-1 and FoxO3A.
- PGC-1 and FoxO3A expression levels decreased in murine aging and OA cartilage (MnX)
**In vitro studies on aging cartilage and chondrocyte senescence**

Aging and oxidative stress reduce the response of human articular chondrocytes to insulin-like growth factor 1 and osteogenic protein 1.

- Age-related decline in proteoglycan synthesis stimulated by IGF-1 (24-81yrs).
- Oxidative stress inhibited IGF-1-stimulated Akt phosphorylation and increased phosphorylation of ERK. These effects were greater in cells from older donors

Depletion of SIRT6 causes cellular senescence, DNA damage, and telomere dysfunction in human chondrocytes.

- The sirtuin, SIRT6, is preferentially expressed in superficial zone chondrocytes (nucleus)
- Depletion of SIRT6 causes cellular senescence, DNA damage, and telomere dysfunction in human chondrocytes
Targeting pro-inflammatory cytokines following joint injury: acute intra-articular inhibition of interleukin-1 following knee injury prevents post-traumatic arthritis.

Closed intra-articular fracture in the lateral tibial plateau of the mouse knee 8 week model of PTOA that is inflammation driven.

Two treatment protocols:
1) Single IA injection of IL-1RA (anakinra) or sTNFRII (etanercept)
2) Systemic administration of IL-1RA or sTNFRII for 4 weeks after fracture

Findings:
• Intra-articular inhibition of IL-1 significantly reduced cartilage degeneration & synovial inflammation.

Significance:
• Supports a role for IL-1, rather than TNF-α, in the acute phase following joint injury
• Acute treatment with local IL1RA can prevent cartilage degeneration and synovitis in PTOA.
Osteoarthritis is a global disease with pathological changes occurring in all the joint tissues. What is the relative contribution at different stages? How do the tissues interact?

Subsets of Osteoarthritis Can be driven by distinct risk factors e.g. obesity, age, PTOA
Specific disease mechanisms?

# Targets under exploration for OA pain (in preclinical studies using OA models)

## CGRP

Peripheral calcitonin gene-related peptide receptor activation and mechanical sensitization of the joint in rat models of osteoarthritis pain.

Bullock CM, Wookey P, Bennett A, Mobasheri A, Dickerson I, Kelly S.


Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain.


*Osteoarthritis Cartilage.* 2014 Apr;22(4):578-85. doi:

## Na-channels, Nav1.7 and Nav1.8

Osteoarthritis-dependent changes in antinociceptive action of Nav1.7 and Nav1.8 sodium channel blockers: An in vivo electrophysiological study in the rat.

Rahman W, Dickenson AH.


## Transient receptor potential cation channel, TRPM2 – sensor for ROS

Involvement of TRPM2 in a wide range of inflammatory and neuropathic pain mouse models.


*J Pharmacol Sci.* 2015 Mar;127(3):237-43. doi:
Thank you