I-14
NEUROVASCULAR CHANGES IN THE OA JOINT
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Purpose: To describe current knowledge leading to a better understanding of OA pain and potential therapeutic targets for symptom and structural modification.

Methods: Narrative review.

Results: Pain originates from the OA joint, mediated by primary nociceptive neurons that have been localised to the majority of articular structures. Fine, myelinated Aδ fibres are localised to joint capsule, periosteum and muscles, whereas unmyelinated C fibres are most abundant with synovium and subchondral bone marrow spaces. Unmyelinated afferents predominantly accompany blood vessels, and serve both sensory (pain) and efferent (control of vascular tone, permeability and proliferation) functions. During OA, sensory nerves change in their distribution, growing with blood vessels into articular cartilage and the inner two thirds of knee menisci. Furthermore, peripheral sensory nerve function is augmented (peripheral sensitisation), accompanied by changes in ion channel phosphorylation, neuromodulator and neurotransmitter expression. Key drivers of peripheral sensitisation offer potential as novel therapeutic targets for OA pain, including nerve growth factor, calcitonin gene-related peptide, and pro-inflammatory cytokines. Neuronal and vascular functions are tightly integrated, with factors originally recognised in pain processing pathways also modulating vascular function, and others, such as vascular endothelial growth factor, now known to also play important roles in neuronal growth and sensitisation. The joint vasculature is key to maintaining articular health, by facilitating metabolic homeostasis, contributing to tissue repair and new bone formation. Inappropriate or inadequate vascular responses might lead to relative hypoxia and acidosis, loss of osteochondral integrity and persistent inflammation; each of which can exacerbate OA pain.

Conclusions: Targeting the neurovascular plasticity that is observed in OA joints might not only afford short term pain relief, but also modify symptomatically relevant structural changes and therefore afford sustained reductions in the burden of OA.

I-15
ROLE OF ZN2+ IMPORT AND THE ZN2+/ZIP8/MTF1 AXIS ON OA
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Osteoarthritis (OA), primarily characterized by cartilage degeneration, is caused by an imbalance between anabolic and catabolic factors. Here, we investigated the role of zinc (Zn2+) homeostasis, Zn2+ transporters, and Zn2+-dependent transcription factors in OA pathogenesis. Among Zn2+ transporters, the Zn2+ importer ZIP8 was specifically upregulated in OA cartilage of humans and mice, resulting in increased levels of intracellular Zn2+ in chondrocytes. ZIP8-mediated Zn2+ influx upregulated the expression of matrix-degrading enzymes (MMP3, MMP9, MMP12, MMP13, and ADAMTS5) in chondrocytes. Ectopic expression of ZIP8 in mouse cartilage tissue caused OA cartilage destruction, whereas ZIP8 knockout suppressed surgically induced OA pathogenesis, with concomitant modulation of Zn2+ influx and matrix-degrading enzymes. Furthermore, MTF1 was identified as an essential transcription factor in mediating Zn2+/ZIP8-induced catabolic factor expression, and genetic modulation of MTF1 in mice altered OA pathogenesis. We propose that the zinc-ZIP8-MTF1 axis is an essential catabolic regulator of OA pathogenesis.

I-16
THE CIRCADIAN CLOCK IN CARTILAGE HOMEOSTASIS
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Purpose: Osteoarthritis (OA) is the most common joint disorder for which age is a major risk factor. We have previously identified autonomous circadian clocks in chondrocytes that become dysregulated with age and in an injury model of OA in mouse. More recently, we have shown that environmental disruption of the circadian rhythm in mice predisposes to OA-like cartilage degeneration in the knee. The objectives were to characterize the circadian clock and their tissue-specific targets in normal, aged and diseased cartilage tissues, and to provide genetic evidence and mechanistic insights linking the chondrocyte circadian clock to cartilage pathologies.

Methods: Cartilage explants were obtained from aged and young mice with the clock reporter PER2::Luc and the real-time bioluminescence recordings were used to characterize the properties of the clock. Time-series microarrays and RNAseq were performed on mouse cartilage tissues to identify rhythmic genes. Experimental OA was induced in mice by destabilization of the medial meniscus (DMM). A Col2a1-Cre driven conditional Bmal1 knockout mouse was made to evaluate the role of circadian clock in cartilage health and disease.

Results: Autonomous circadian clocks in mouse cartilage tissue and human chondrocytes were identified, which can be entrained by systemic factors such as body temperature rhythms. The circadian and diurnal transcriptomes in mouse cartilage revealed a large number of rhythmic genes involved in cartilage homeostasis and chondrocyte survival. Several clock genes were disrupted in the early stages of cartilage degeneration in the DMM mouse model of OA, as well as in human OA samples. Further, the conditional chondrocyte-Bmal1 knockout model caused no developmental abnormalities in the articular cartilage although significant pathology became apparent in the adult articular cartilage. RNAseq revealed global changes in gene expression that favours a more catabolic state of the Bmal1 KO chondrocytes.

Conclusions: These results reveal an autonomous circadian clock in chondrocytes that is implicated in key aspects of cartilage tissue homeostasis and chondrocyte health. We envisage a scenario where chronic circadian disruption or misalignment (e.g., during aging) may compromise cartilage tissue homeostasis and increase susceptibility to joint damage or disease. Further investigations may lead to novel targeting strategies for joint diseases, including timed drug administration (chronotherapy), or the use of circadian clock-acting compounds.

I-17
HOW CAN DISTURBANCES OF THE NERVOUS SYSTEMS TRANSLATE IN OA PHENOTYPES?
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Osteoarthritis has long been considered as a joint disease influenced by local factors only (such as overload, joint trauma or anatomical deformities) which would trigger cartilage, subchondral bone and synovial cells activation leading to the release of degradative mediators eventually destroying the matrix. More recently, observational and interventional experimental studies have shown that a systemic low-grade inflammation component could play an additional role, at least in a subgroup of OA patients suffering from metabolic diseases like obesity, diabetes mellitus, lipid abnormalities or hypertension. Because of the recent knowledge about close connections between inflammation, metabolic diseases and the brain, the influence of nervous system pathways on initiation and/or progression of OA could be considered, too. In this lecture, these potential pathways involved in communications between OA joints and the nervous system will be presented. The role of the circadian rhythms and of the autonomic nervous system on the pathophysiology of OA will be particularly developed. Such an integrative vision of the OA process is changing our paradigm by including OA in the list of the metabolic diseases that could be influenced by the brain. If confirmed, this hypothesis could be a breakthrough for treating OA, by seeking new targets modulating these pathways. A cross-cutting approach of the pathophysiology of the disease is now inevitable for a step-forward in the treatment approach of OA in the future.
The document contains text about osteoarthritis (OA) research, focusing on the role of thyroid hormones and genetic factors. It discusses the development of OA and the potential for targeted treatments. The text mentions the importance of understanding the molecular processes that lead to OA and the role of epigenetic factors, such as thyroid hormone levels, in the disease progression. It also highlights the need for more human-focused research and the potential of new therapeutic options based on recent findings.