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Review

Osteoarthritis year in review 2016: biology

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SUMMARY

This review highlights a selection of literature in the area of osteoarthritis biology published between the 2015 and 2016 Osteoarthritis Research Society International (OARSI) World Congress. Highlights were selected from a pubmed search covering cartilage, bone, inflammation and pain. A personal selection was made based, amongst other things, on topics presented during the 2015 conference. This covers circadian rhythm, TGF-β signaling, autophagy, SIRT6, exercise, lubricin, TLR's, pain and NGF. Furthermore, in this review we have made an effort to connect these seemingly distant topics into one scheme of connections between them, revealing a theoretical big picture underneath.

Introduction

For this year in review in osteoarthritis biology we made a personal selection of the articles from pubmed searches on “osteoarthritis and cartilage”, “osteoarthritis and inflammation”, and “osteoarthritis and subchondral bone”. The selection was further based on topics that were selected for presentation during the Osteoarthritis Research Society International (OARSI) 2015 conference as well as on topics that were researched by multiple groups in this year. We made an effort to interconnect the mechanisms these articles describe to osteoarthritis pathophysiology. This led to addition of a few articles that revealed the connecting elements. This grand scheme of interactions formed the foundation for this review (Fig. 1).

Circadian rhythm

Cartilage degradation is a hallmark of OA. This year, great progress has been made in understanding the role of the circadian clock in cartilage homeostasis, and how dysregulation hereof can result in cartilage degradation and OA. Circadian rhythms are physical, mental and behavioral changes that respond primarily to light and dark and hence roughly follow the 24-h light–dark cycle. It has become clear that this cycle is also present in cells that do have the ability to perceive light and dark themselves, but rely on so-called clock genes to synchronize cellular processes. Recently, it has become clear that these synchronizing processes are important in chondrocyte behavior.

Kc *et al.* compared mice with a standard 12 h light and dark cycles, with mice where this cycle was reversed at the end of each week for the duration of 22 weeks[1]. This shift in cycle resulted in a reduced proteoglycan content, increased fibrillation and a higher OARSI histopathology score, indicating increased OA severity. Remarkably, when a high fat diet (HFD) was added during the final 10 weeks of the protocol, the differences between non-shifted and shifted were further increased, illustrating a link between circadian rhythm and metabolism. When this group investigated which clock genes could be involved by mutating either *Clock* or CSK1 epsilon tau in mice, remarkably, neither of these mutations resulted in joint pathology[2]. In contrast, Dudek *et al.* showed that disruption of another core clock gene, BMAL1, does result in joint damage. BMAL1 was reduced in OA cartilage with increasing severity as well as with aging[3]. By generating a chondrocyte-specific *Bmal1*-KO mouse they disrupted the circadian clock activities in cartilage tissues and as a result found progressive degeneration and lesions in knee articular cartilage from age 2 months on and by 3–6 months this had resulted in severe lesions. Furthermore, with RNA-Seq they screened for possible mechanisms to explain how clock disruption results in OA. With this technique they found that TGF-β receptor ALK1 (Acvrl1) levels were rhythmic in WT mice, but constantly upregulated in the conditional Bmal1-KO mouse at night, while ALK5 (Tgfbr1) levels remained unchanged. This suggested a change to increase in the Alk1/Alk5 ratio which has previously been identified as catabolic for cartilage and associated

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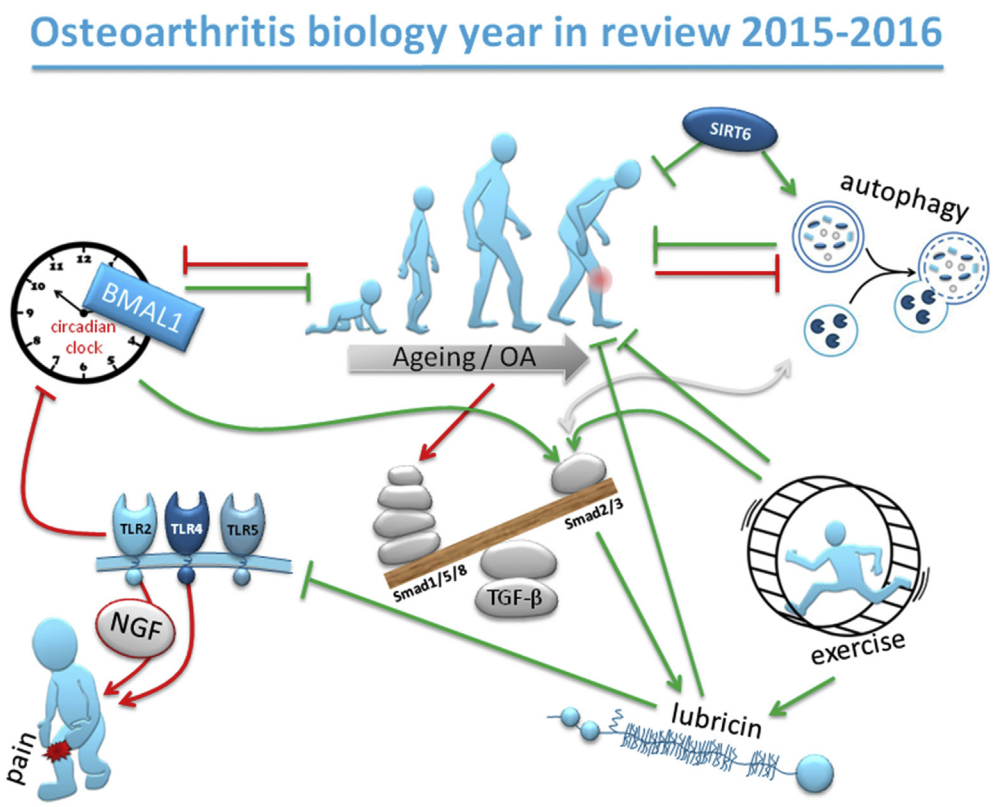

Fig. 1. Scheme of the osteoarthritis biology year in review 2015–2016. This is a simplified scheme of the connections between findings reported in studies selected for this year in review. Connections indicated in green have a positive outcome on OA, whereas those in red have a negative outcome. Arrows indicate stimulation, blocked lines indicate inhibition. This scheme is simplified in such a way that aging and OA are in one frame, but not necessarily connected. Content of this scheme is summarized in the conclusion section of this review.

with OA[4]. This was further confirmed with corresponding downstream alterations: decreased Smad2 but increased Smad1/5 phosphorylation as well as altered expression of downstream markers in conditional Bmal1-KO. In addition, Nfat7c2, which was recently identified as a key chondrocyte transcriptional marker for healthy cartilage, was also reduced in the conditional Bmal1-KO.

Guo *et al.* studied the function of the core Clock/BMAL complex in chondrocyte-like cells and cartilage from a Cry1-luc mouse, which is a reporter for circadian rhythm. They found that addition of the pro-inflammatory factors IL1β or LPS, but not the addition of TNFα, disturbed the circadian rhythm by dampening it. This was reversible by adding the anti-inflammatory and synchronizing agent dexamethasone, but not by other synchronizing agents. Mechanistically it was shown that IL1β disrupted the Clock/Bmal1 complex in an NFκB dependent manner. Strikingly, the inhibitory effect of IL1 and LPS was not observed in tissue explants from lung or esophagus, suggesting perhaps a cartilage-specific mechanism.

Together these studies show that the genes involved in the circadian rhythm, in particular Bmal1, is important for cartilage maintenance and that disruption thereof, which can be achieved by a pro-inflammatory environment, could be involved in OA. Downstream of this circadian rhythm disruption lies the disturbance of cartilage-maintenance factors Nfatc2 and TGF-β signaling.

TGF-β signaling

This year many researchers have focused on modulating TGFβ signaling as a potential therapeutic application in OA. As stated before, TGF-β can signal via multiple pathways. The receptors bound by TGF-β govern the downstream signals, hence ALK5 binding leads to Smad2/3 signaling which is associated with a beneficial, maintenance effect on cartilage, whereas ALK1 binding leads to Smad1/5/8 signaling ultimately driving factors associated with chondrocyte hypertrophy. Jeffries *et al.* investigated which pathways and upstream regulators are shared by differentially methylated genes in both OA subchondral bone and cartilage[5]. Strikingly, TGF-β was on top of that list, followed by TNF and p53, further establishing TGF-β as a key player in OA. Xie *et al.* blocked TGF-β systemically by i.p. injection with a neutralizing antibody (1D11) and found that it attenuated ACLT-induced OA in mice[6]. The antibody treatment resulted in decreased thickness of calcified cartilage, reduced proteoglycan loss, slowed degeneration of articular cartilage and improved subchondral bone structure in ACLT mice as compared to vehicle-treated ACLT mice. It is important to note the author statement that the high dose of the antibody resulted in thinner hyaline cartilage and proteoglycan loss, indicating that a certain level of TGF-β should remain in order to preserve bone and cartilage integrity. Interestingly, the levels of phosphorylated Smad2/3, which are indicative of active TGF-β signaling, were reduced in ACLT cartilage and increased in subchondral bone. Treatment with the antibody resulted in reduced phosphorylated Smad2/3 in the subchondral bone, whereas in ACLT cartilage it resulted in less pronounced reduction than ACLT alone. Unfortunately, the authors did not comment on a potential mechanism.

Zhao *et al.* focused on cartilage degeneration and excessive subchondral bone formation in spontaneous OA in Dunkin-Hartley guinea pigs[7]. Doing so, they confirmed earlier findings: a switch in the expression of phosphorylated Smad2/3 to Smad1/5/8 in degenerating cartilage during chondrocyte terminal differentiation.