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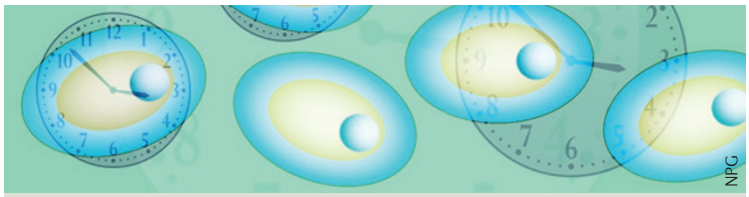

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Chondrocyte clock maintains cartilage tissue

A core component of the circadian clock, the transcription factor brain and muscle Arnt-like protein 1 (BMAL1, also known as aryl hydrocarbon receptor nuclear translocator-like protein 1), contributes to the homeostasis of articular cartilage according to a paper now published in *The Journal of Clinical Investigation*. The results of the study suggest that disruption of chondrocyte BMAL1 or of the circadian rhythm could be a contributing factor to the development of osteoarthritis (OA).

"We have shown previously that mouse and human chondrocytes contain autonomous circadian clocks, which temporally segregate the activity of key catabolic and anabolic pathways to different times of the day," explains Qing Jun Meng, one of the corresponding authors of the current study. "The local cartilage clock becomes weaker with ageing and is dysregulated by chronic inflammation; moreover, environmental disruption of circadian rhythm can act as a predisposing factor for OA-like pathologies in a mouse model," Meng continues. Although these earlier findings suggested a role for circadian rhythm in cartilage health, definitive evidence was lacking. Combining analyses of tissue samples from patients with OA and aged mice, as well as a chondrocyte-specific *Bmal1*-knockout mouse model (generated by crossing *Col2a1*^{cre} mice with *Bmal1*$^{fl/fl}$ mice), the latest study identifies clock-controlled genes in cartilage and demonstrates an essential role for BMAL1 in cartilage homeostasis."These findings provide the first genetic evidence linking a core clock factor to the health and disease of the articular cartilage," adds co-corresponding author Ray Boot-Handford.

The investigators first demonstrated that BMAL1 expression in articular cartilage from the knees of patients with OA is negatively correlated with disease severity, and that the number of BMAL1-positive chondrocytes is reduced in knee cartilage from aged mice (22–24 months) as compared with young mice (2–3 months). Using a clock gene reporter (PER2::Luc) mouse model, they then confirmed that chondrocyte-specific knockout of *Bmal1* abolishes the circadian rhythm in cartilage tissues, but not in the brain, lung or heart.

Notably, these *Bmal1*-knockout mice had progressive degeneration of knee articular cartilage but normal subchondral bone, synovium and ligaments. Moreover, RNA sequencing (RNA-seq) analysis demonstrated that loss of *Bmal1* in chondrocytes was associated with dysregulation of the rhythmic patterns of several genes relevant to cartilage homeostasis and OA. "We used circadian time series RNA-seq studies, which enabled us to reveal genome-wide changes of the rhythmic patterns of cartilage transcriptome between wild-type and *Bmal1*-knockout cartilage," explains Boot-Handford. Further experiments determined that TGF-β signalling is dysregulated in cartilage from *Bmal1*-knockout mice, as is circadian control of the NFATC2 pathway.

"While a connection between circadian rhythms and OA has been established for a while, this study provides a lot of novel and exciting molecular insights into the underlying mechanisms," comments Frank Beier of the University of Western Ontario, who was not involved in the study. "The identification of a number of downstream pathways affected is also intriguing but warrants further studies as clear functional connections need to be established."

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