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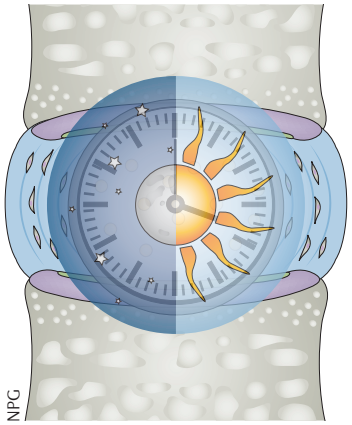
MUSCULOSKELETAL SYSTEM

Catching the rhythm of disc degeneration

> [these findings] provide the first genetic evidence linking a core clock factor to the health and disease of the spinal disc

A molecular clock regulated by age and inflammatory cytokines is present in intervertebral disc (IVD) tissues, and targeted deletion of *ARNTL* (encoding aryl hydrocarbon receptor nuclear translocator-like protein 1, also known as BMAL1) in mice results in IVD degeneration, according to a new study by Qing-Jun Meng and colleagues. "These findings reveal for the first time the molecular and cellular mechanisms of the circadian clock within the disc tissue, and provide the first genetic evidence linking a core clock factor to the health and disease of the spinal disc," says Meng, corresponding author of the study.

Epidemiological evidence indicates an association between factors known to disrupt circadian rhythms and sleep, such as shift work, and the risk of IVD degeneration and low back pain. "The spinal disc is a highly rhythmic tissue, experiencing daily cycles of loading, followed by a period of low-load recovery. These observations strongly suggest a role of circadian rhythms in the maintenance of disc health. However, experimental evidence of autonomous circadian clocks in the disc was lacking before this current project," explains Judith Hoyland, co-corresponding author of the study.



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To visualize the local molecular clock in real time, the investigators performed quantitative bioluminescence imaging of clock gene reporters in mouse IVD explants. The levels of core clock factors BMAL1 and circadian locomoter output cycles protein kaput (CLOCK), and the oscillation amplitude of the molecular clock, were progressively reduced with advancing age in mice. Furthermore, the IVD circadian clock was disrupted by the proinflammatory cytokine IL-1β via nuclear factor-κB (NF-κB), but not by TNF. Meng also points out that loss of *BMAL1* in conditional knockout mice led to progressive disc degeneration, similar to what is seen in human degenerative discs.

The researchers are now planning to investigate how the clock factors change in human degenerative discs, and study the causal relationship between circadian rhythm disruption and low back pain. "Further investigation holds potential to advance our understanding of the pathogenesis of disc degeneration. This knowledge may also help to improve current treatment strategies for low back pain, such as the timing of drug delivery according to the clock time of the disc," concludes Hoyland.

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ORIGINAL ARTICLE Dudek, M. *et al.* The intervertebral disc contains intrinsic circadian clocks that are regulated by age and cytokines and linked to degeneration. *Ann. Rheum. Dis.* http://dx.doi.org/10.1136/annrheumdis-2016-209428 (2016)