It's all about the timing: Fetal expression of core clock gene determines lifespan in mice

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Is the molecular clock essential to retard aging? Credit: Guangrui Yang PhD, Perelman School of Medicine, University of Pennsylvania

Abolishing the 24-hour clock by knocking out a key gene during development accelerates aging and shortens lifespan by two thirds in mice, but this effect is absent if the gene deletion is delayed until after birth, according to a new study published this week in *Science Translational Medicine* by scientists from the Perelman School of Medicine at the University of Pennsylvania.

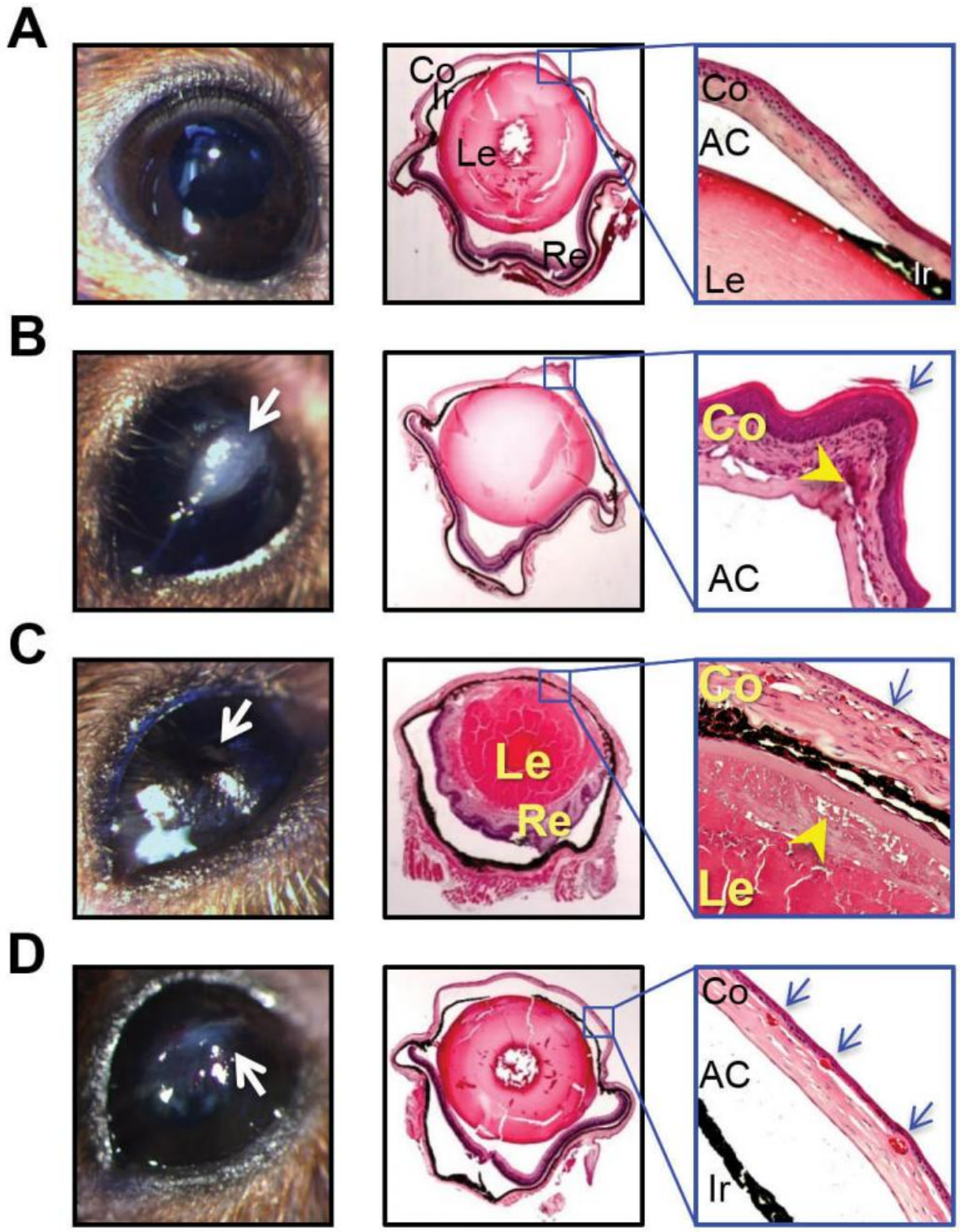
As humans age, biological rhythms flatten, slow down, and eventually stop. Whether this relationship between aging and the molecular clock that drives such rhythms reflects cause or effect is unknown. To assess the role of the molecular clock in aging, Penn researchers, led by senior author Garret A. FitzGerald MD, chair of the department of Systems Pharmacology and Translational Therapeutics, made conditional Bmal1 knockout mice missing the BMAL1 protein only during adult life and compared them with conventional knockouts in which the gene is absent during development.

In both cases, the clock was paralyzed. Cyclical variation in gene expression, behavior, and blood pressure was abolished. However, while some effects suggestive of aging were common to both strains of mice - cataracts and signs of neurodegeneration - others, including lifespan, fertility, and signs of arthritis were absent when Bmal1 deletion was delayed until after birth. Indeed, in some cases - such as the capacity for hair regrowth after shaving - the impact of the knockout was reversed.

Analysis of gene expression showed that while both knockouts stopped genes oscillating in a circadian rhythm, the conventional knockouts also changed the overall expression of many non-cycling genes, which functionally may explain the divergent findings.

"Others have found that the Bmal1 gene, although expressed early, only

begins to oscillate late in development, so many of the consequences of deleting the gene early may reflect off-target effects, unrelated to its role in the clock," said Guangrui Yang PhD, co-first author and a research assistant professor in Pharmacology. However, he added future studies aim to elucidate when and if Bmal1 begins to function as a clock gene in utero.



Ocular abnormalities and astrogliosis in inducible Bmal1 knockout (iKO) mice. Representative gross images (left) and hematoxylin and eosin (H&E)–stained sections of eyes (middle and right) from Ctrl (A) and iKO mice (B to D). (A)

Unremarkable globe from a Ctrl mouse. AC, anterior chamber; Co, cornea; Ir, iris; Le, lens; Re, retina. (B) Pathologic changes in a male mouse eye. Grossly, there is a leukoplakic plaque on the cornea (left, arrow). Histologically, the cornea appears thickened with keratinization of the epithelium (right, arrow) and chronic inflammation and neovascularization of the stroma (right, arrowhead). (C) In the contralateral eye of the same mouse, the corneal surface appears irregular with a flattened chamber. Histologically, the cornea appears thickened. The retina is adherent to the lens. The corneal epithelium is attenuated (right, arrow) with chronic inflammation and neovascularization in the stroma. A subcapsular anterior cataract is present (right, arrowhead). (D) A female mouse eye shows an irregular corneal surface with leukoplakia (left, arrow) and corneal neovascularization (right, arrow). Credit: G. Yang et al., Science Translational Medicine (2016)

The conventional knock out of Bmal1 has been used extensively to implicate the molecular clock in body functions and disease. The findings prompt reconsideration of these assumptions and highlight the need to understand the role of clock genes during development.

"Indeed, the importance of Bmal1 expression during development in the determination of lifespan is reminiscent of the Barker hypothesis, which postulates that the fetal environment influences disease expression and lifespan in humans after birth," FitzGerald suggested. "The Barker hypothesis has been thought to reflect the epigenetic impact of maternal exposures, such as to cigarettes, alcohol, or toxins in the environment. Given the anticipatory role of the clock, an intriguing possibility raised by these findings is that the timing of such exposures might modulate their impact on postnatal life."

More information: "Timing of expression of the core clock gene Bmal1 influences its effects on aging and survival," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aad3305

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