Ground squirrel study points to potential development of a cataract drug

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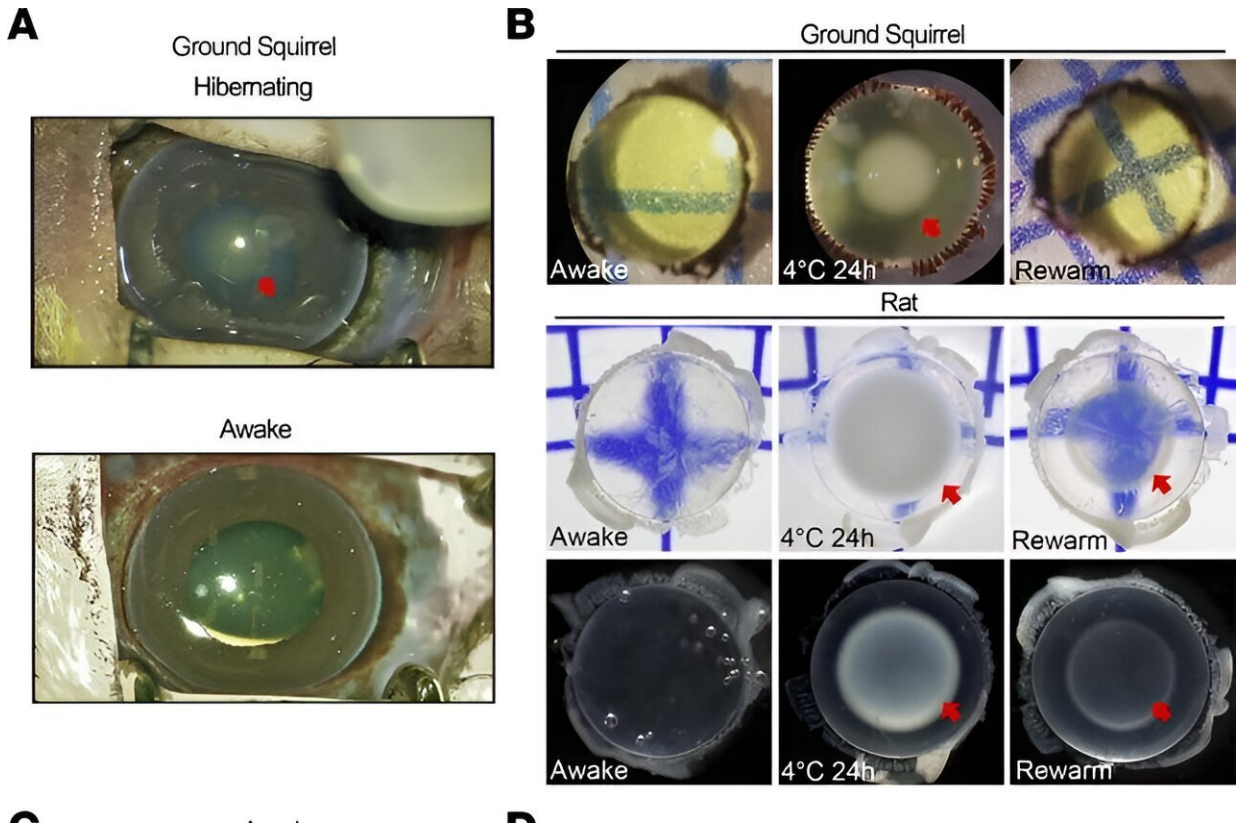

GS lens opacity is reversed during the hypothermia-rewarming cycle. Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169666

Researchers at the National Institutes of Health (NIH) and their collaborators have identified a protein, known as RNF114, that reverses

cataracts, a clouding of the eye's lens that occurs commonly in people as they age. The study, which was conducted in the 13-lined ground squirrel and rats, may represent a possible surgery-free strategy for managing cataracts, a common cause of vision loss. The study published in the *Journal of Clinical Investigation*.

"Scientists have long searched for an alternative to cataract surgery, which is effective, but not without risk. Lack of access to cataract surgery is a barrier to care in some parts of the world, causing untreated cataracts to be a leading cause of blindness worldwide," said Xingchao Shentu, M.D., a cataract surgeon and the co-lead investigator from Zhejiang University, China.

This new discovery was part of ongoing research at NIH's National Eye Institute (NEI) involving a mammalian hibernator, the 13-lined ground squirrel. In these ground squirrels, the light-sensitive photoreceptor cells in the retina are mostly cones, which makes the ground squirrel helpful for studying cone-related properties, such as color vision. In addition, the squirrel's ability to withstand months of cold and metabolic stress during hibernation make it model for vision scientists to study a range of eye diseases.

Researchers learned that during hibernation, the ground squirrel's lenses became cloudy at around 4 degrees Celsius but quickly turned transparent after rewarming. By comparison, non-hibernators (rats in this study) developed cataracts at low temperatures, but they did not resolve with rewarming.

Cataract formation in hibernating animals exposed to low temperatures is likely a cellular response to cold stress and is one of many changes their bodies undergo as their tissues adapt to freezing temperatures and metabolic stress. Humans do not develop cataracts when exposed to low temperatures.

"Understanding the molecular drivers of this reversible cataract phenomenon might point us in a direction toward a potential treatment strategy," said the study's co-lead investigator, Wei Li, Ph.D., senior investigator in the NEI Retinal Neurophysiology Section.

The main job of the lens is to focus light onto the retina at the back of the eye. As we age, cataracts form when proteins in the lens start misfolding and forming clusters that block, scatter, and distort light as it passes through the lens. For reasons that are not clear, aging can disrupt protein homeostasis—a process that maintains the balance of newly made proteins and the turnover of old proteins.

To explore the ground squirrel's reversible cataracts at the molecular level, the team developed a lab-based, lens-in-a-dish model using stem cells engineered from ground squirrel cells by the Li Lab at NEI. Using this platform, the researchers zeroed in on a part of an extensive network that maintains protein homeostasis in part by breaking down old proteins, known as the ubiquitin proteasome system.

Specifically, RNF114 was significantly elevated during rewarming in the ground squirrel, compared with the non-hibernating rat. RNF114 had previously been shown to help identify old proteins and facilitate their degradation.

To look further at RNF114's effect, they again used a non-hibernator (rat) cataract model by incubating its lenses at 4 degrees Celsius. Normally, such cataracts would not resolve with rewarming. However, when the lenses were pretreated with RNF114, there was a rapid clearing of the cataract upon rewarming.

According to the scientific team, these findings are proof-of-principle that it is possible to induce cataract clearance in animals. In future studies, the process will need to be fine-tuned so scientists can stimulate

specific protein degradation to see how to precisely regulate protein stability and turnover. This mechanism is also an important factor in many neurodegenerative diseases, they said.

More information: Hao Yang et al, Reversible cold-induced lens opacity in a hibernator reveals a molecular target for treating cataracts, *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169666

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