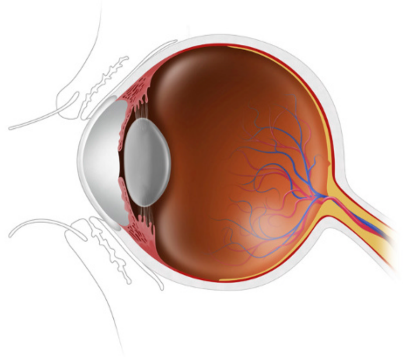
Clearing cataracts without surgery

Cataracts cause blindness in tens of millions of people worldwide, and currently can be treated only with surgery. Cataracts form owing to aggregation of proteins in the lens of the human eye. This lens is made up of a complex crystalline protein array that gives it transparency and its refractive index. The major structural proteins of the lens are called crystallins, and mutations can cause crystallins to aggregate and form cataracts. The mechanisms underlying this aggregation of proteins in cataracts (and its absence in healthy lenses) are not well understood.

In a recent paper published in *Nature* (doi:10.1038/nature14650; published online 22 July 2015), Kang Zhang (University of San Diego, CA) and colleagues identified mutations in a gene, lanosterol synthase (LSS), in two families with congenital cataracts. Further experiments in cells and in animals showed that LSS regulates aggregation of cataract-forming proteins and identified a potential non-surgical treatment for cataracts.

LSS synthesizes lanosterol, a molecule that is part of the cholesterol synthesis pathway. Lanosterol is enriched in the eye's lens and



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the mutations identified by Zhang and colleagues affect the ability of LSS to catalyze the formation of lanosterol. In cells expressing mutant crystallin proteins, existing protein aggregation was reduced by expression of wildtype LSS, but the mutant forms identified in the human families did not reduce aggregation. *In vitro* experiments showed that lanosterol itself could dissolve aggregated crystallin proteins. Encouraged by their *in vitro* results, the researchers tested lanosterol's efficacy in more clinically relevant models. They found that application of lanosterol increased the transparency of dissected cataractous lenses from rabbits, and it successfully decreased cataract severity in dogs.

These findings represent a significant advancement in our understanding of how cataract formation is prevented in healthy eyes. Perhaps more excitingly, they suggest a simple and noninvasive treatment for cataracts, although further research is required before this could be tried in humans. The study is also an excellent example of the power of genetics to inform biological understanding and development of new therapeutics. As one of the authors, Dr. Xin Jin (BGI-Shenzhen, Shenzhen, China), said in a press release, "This project is aimed to discover [casual] genes for congenital cataracts. Then we uncovered that [the] gene LSS [was] responsible for two affected families involved in the study. This is extremely exciting when we noticed that the discovery might lead to a novel and simple strategy for the prevention and treatment of cataracts. It encourages us to have more efforts from bench to bedside."

Brigitta B. Gundersen

COGNITIVE TRAINING DETERS DRUG-SEEKING IN MICE

Drug abuse is an expensive and destructive threat to public health. People who experience environmental stress or live in conditions of poverty are generally more vulnerable to abusing drugs. Similar factors also promote drug-seeking behavior in animal models. "We know that mice living in deprived conditions show higher levels of drug-seeking behavior than those living in stimulating environments," said Josiah Boivin (University of California, San Francisco) in a recent press release.

The ability to control one's environment can counteract this vulnerability, buffering the effects of deprivation and potentially reducing unhealthy responses to drugs of abuse. Cognitive training with active learning is one way to provide a sense of control that could promote resilience to drug abuse. Together with Linda Wilbrecht (University of California, Berkeley) and Denise Piscopo (University of Oregon, Eugene), Boivin carried out a study to test this possibility in mice, finding that exposure to a stimulating learning environment lessened drug-seeking behavior.

The study involved three groups of mice. The first group underwent a 9-day cognitive learning program in which they were trained to locate and retrieve a food reward within an arena that was enriched with sensory stimuli. Each mouse in the second group was 'yoked' to a mouse in the first group: placed in an identical, adjacent arena and given the same food reward each time its trained partner earned a food reward. The third group of mice remained in their home cages during the training period and did not undergo cognitive training or receive food rewards. Four weeks later, the scientists exposed all the mice to cocaine and then evaluated their drug-seeking behavior. The trained mice and the yoked mice both showed reductions in drug-seeking behavior, and the benefit was greater in trained mice than in yoked mice (*Neuropharmacol*. **97**, 404–413; 2015). The beneficial effects of training persisted for weeks after the training period.

These findings suggest that deprivation might increase vulnerability to drug-seeking behavior and, conversely, cognitive training might boost long-term resilience to future substance abuse. Such results could have promising implications for averting drug abuse in humans, if future research shows that active learning has similar effects in people. "Our data are exciting because they suggest that positive learning experiences, through education or play in a structured environment, could sculpt and develop brain circuits to build resilience in at-risk individuals," Wilbrecht explained in a press release.

Monica Harrington