Medical Xpress

Study finds eye color genes are critical for retinal health

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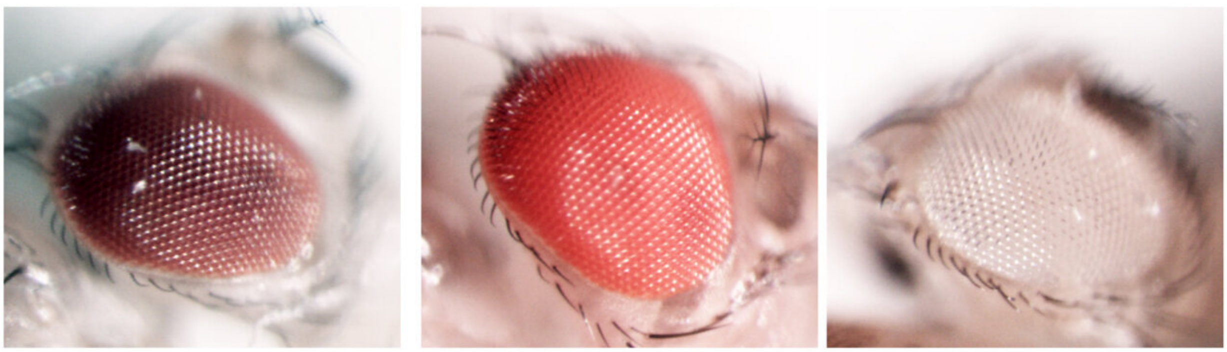

Photos of fly eyes with different colors ranging from normal (left, red) to abnormal (bright red, middle, mutation in the cinnabar gene), and white, right (mutation in the white gene). Abnormal eye color arises due to mutations in genes that regulate pigment formation and a specific metabolic pathway. Credit: Hebbar et al, *PLOS Genetics*, 2023 / MPI-CBG

Metabolic pathways consist of a series of biochemical reactions in cells that convert a starting component into other products. There is growing evidence that metabolic pathways coupled with external stress factors influence the health of cells and tissues. Many human diseases, including retinal or neurodegenerative diseases, are associated with imbalances in metabolic pathways.

Elisabeth Knust led a team of researchers from the Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG) in Dresden, Germany, who described an essential role for one such metabolic pathway in maintaining retinal health under conditions of stress. They studied the classic Drosophila genes cinnabar, cardinal, white, and scarlet, originally characterized decades ago and named due to their role in eye color pigmentation, in particular the formation of the brown pigment of the fly eye.

These genes encode components of the kynurenine pathway, whose activity converts the amino acid tryptophan by various steps into other products. In this study, the authors have highlighted the function of this metabolic pathway in retinal health, independent of its role in pigment formation.

The Kynurenine pathway is an evolutionary conserved metabolic pathway that regulates a variety of biological processes. Its disruption can result in the buildup of either toxic or protective biomolecules or metabolites, which can worsen or improve, respectively, the health of the brain, including the retina. Knowledge of this important metabolic pathway was recently extended by the research team, led by Knust, Director Emerita at the MPI-CBG, in their publication in the journal *PLOS Genetics*.

Being aware of the remarkable conservation of this metabolic pathway and the genes that regulate it, they used flies as a model system to unravel the role of individual metabolites in retinal health. The researchers looked at four genes—cinnabar, cardinal, white, and scarlet—named after abnormal eye colors following their loss in flies. "Since the Kynurenine pathway is conserved from flies to humans, we asked whether these genes regulate retinal health independent of their role in pigment formation," says Sarita Hebbar, one of the lead authors of the study.

To find this out, the scientists used a combination of genetics, dietary changes, and biochemical analysis of metabolites to study different mutations of the fruit fly, Drosophila melanogaster. Sofia Traikov, a co-author, developed a method for the biochemical analysis of the metabolites of the Kynurenine pathway. This allowed the researchers to link different metabolite levels to the health state of the retina. They found that one metabolite, 3-hydroxykynurenine (3OH-K), is damaging to the retina. More importantly, they could show that the degree of degeneration is influenced by the balance between toxic 3OH-K and protective metabolites, such as Kynurenic Acid (KYNA), and not just by their absolute amounts.

Sarita adds, "We also fed two of these metabolites to normal (non-mutant) flies and found that 3OH-K enhanced stress-induced retinal damage, whereas KYNA protected the retina from stress-related damage." This means that retinal health in certain conditions can be improved by altering the ratio of metabolites of the Kynurenine pathway.

Furthermore, by targeting these four genes and therefore four distinct steps within the pathway, the researchers were able to demonstrate that not only the accumulation of 3OH-K as such, but also its location in the cell and hence its availability in further reactions, is important for retinal health.

"This work shows that the Kynurenine pathway is important not only in pigment formation but that the level of individual metabolites fulfills important roles in maintaining retinal health," says Knust. "In the future, the ratio of the various metabolites and the specific sites of their accumulation and activity should be taken into account in therapeutic strategies for diseases with impaired Kynurenine pathway function, observed in various neurodegenerative conditions."

More information: Sarita Hebbar et al, Modulating the Kynurenine pathway or sequestering toxic 3-hydroxykynurenine protects the retina from light-induced damage in Drosophila, *PLOS Genetics* (2023). DOI: 10.1371/journal.pgen.1010644

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