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MicroRNAs appear essential for retinal health

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Retinas in newborn mice appear perfectly fine without any help from tiny bits of genetic material called microRNAs except for one thing — the retinas do not work.

In the first-ever study of the effects of the absence of microRNAs in the mammalian eye, an international team of researchers directed by the University of Florida and the Italian National Research Council describes a gradual structural decline in retinas that lack microRNAs — a sharp contrast to the immediate devastation that occurs in limbs, lungs and other tissues that develop without microRNAs.

The discovery, reported in today's (May 7) issue of the *Journal of Neuroscience*, may lead to new understanding of some blinding diseases and further penetrates the cryptic nature of microRNAs — important gene regulators that a decade ago were considered to be little more than scraps floating around the cell's working genetic machinery.

"MicroRNAs are behaving differently in the nervous system than they are in other bodily tissues," said Brian Harfe, Ph.D., an assistant professor of molecular genetics and microbiology at the University of Florida College of Medicine. "Judging by our previous studies in limb development, I was expecting to see lots of immediate cell death in the retina. I was not expecting a normal-looking retina in terms of its form. It would be something like finding a perfectly formed arm at birth that just did not work."

Production of microRNAs is dependent on Dicer, an enzyme widely used by living things to kick-start the process of silencing unwanted genetic messages. By breeding mice that lack one or both of the forms — or alleles — of the gene that produces Dicer in the retina, scientists were able to observe retinal development when Dicer levels were half of normal or completely eliminated.

Electrical activity in retinas devoid of Dicer was abnormally low at the time of eye opening and became progressively worse at 1-, 3- and 5-month stages. Structurally, the retinas initially appeared normal, but the cells progressively became disorganized, followed by widespread degeneration.

Retinas in animals equipped with a single form of the Dicer gene never underwent the inexorable structural decline that occurs in total absence of Dicer, but they also never functioned normally, according to electroretinograms.

“We have removed Dicer from about 30 different tissues,” said Harfe, a member of the UF Genetics Institute. “In all of those cases with half the amount of Dicer, you still had a normal animal. In the retina, there were functional abnormalities. This is the first indication that the dose of Dicer is important for normal retinal health.”

Inherited forms of retinal degeneration affect about 100,000 people in the United States, according to the National Eye Institute. The problems typically occur with the destruction of photoreceptor cells called rods and cones in the back of the eye. More than 140 genes have been linked to these diseases, which only account for a fraction of the cases.

“We have many types of retinal degeneration and not enough mutations to explain them,” said Enrica Strettoi, a senior researcher at the Institute of Neurosciences of the Italian National Research Council in Pisa, Italy.

“Finding that ablation of Dicer causes retinal degeneration might be helpful in discovering candidate disease genes. What we’ve done is target virtually all microRNAs in the retina by ablating Dicer, the core enzyme regulating their synthesis. The next step is to try to address each one separately, and find the role of specific microRNAs. Removal of Dicer from other areas of the central nervous system has also produced functional and structural abnormalities, confirming the fundamental role of this enzyme in neurons.”

More than 400 microRNAs have been identified in both mice and humans, and each one has the potential to regulate hundreds of target genes. They have also been linked to human diseases such as diabetes, hepatitis C, leukemia, lymphoma, Kaposi’s sarcoma and breast cancer.

“This interesting study, together with recent findings reported from three other labs in the United States, provide strong evidence that the microRNA pathway is involved in the health and sickness of many parts of the mammalian nervous system,” said Fen-Biao Gao, an investigator at the Gladstone Institute of Neurological Disease at the University of California-San Francisco, who did not participate in the research. “Additional in-depth studies in the future will likely help develop new therapeutic approaches for many neurodegenerative diseases.”

Source: University of Florida