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Researchers find eye development error causing cataracts, glaucoma

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A Jackson Laboratory research team, working in collaboration with researchers at Brigham and Women's Hospital and Harvard Medical School in Boston, show that RNA granules--key players in messenger RNA (mRNA) processing--can affect eye development, leading to juvenile cataracts in humans and mice.

The research, published in the March 25 issue of *Science*, also demonstrates the first connection between RNA granules and glaucoma, as the humans and mice in the study developed glaucoma.

In the laboratory of Jackson Professor and Howard Hughes Medical Institute Investigator Simon John, Ph.D., study coauthors Stephen Kneeland, Ph.D., and Gareth Howell, Ph.D., identified a malfunctioning gene in a mouse strain that develops both cataracts and glaucoma. The gene, Tdrd7, fails to build an essential protein and disrupts the development of the mouse eye lens. Mice missing the protein developed high intraocular pressure and optic nerve damage--the hallmarks of glaucoma--as well as cataracts.

The John team learned that Salil A. Lachke, Ph.D., of Brigham and Women's Hospital and Harvard Medical School, then a research fellow in the laboratory of Richard L. Maas, M.D., had found the same malfunction in a study of genetic data from patients with pediatric cataracts.

The research teams combined forces and discovered that the protein

missing in the children and the mice belongs to a type of structure known as RNA granules. RNA granules function to regulate mRNAs in the cell. mRNA's primary job is to serve as a template to carry DNA-encoded information from the nucleus into the cytoplasm or body of the cell, providing the blueprints for protein production. The TDRD7 mutation affects mRNA regulation, and this misregulation was implicated in causing the cataracts. Furthermore, the human patients developed glaucoma following cataract extraction.

TDRD7 deficiency greatly reduces the number of stress granules that are produced in lens cells in response to oxidative stress, the researchers show. Stress granules, a specific type of RNA granule, are important to protect the cell in stressful conditions. Oxidative stress has been previously suggested to contribute to glaucoma by damaging the ocular drainage structures. The new findings imply that mice and patients with these mutations may not have adequate protection from oxidative stress in the drainage structures of the eye. With increasing age, their tissues may be more susceptible to oxidative damage resulting in high intraocular pressure and glaucoma.

Although further experiments are needed to be certain, this work is the first to suggest that RNA granules are important in modulating the oxidative stress response relevant to glaucoma. John notes, "There is a growing body of literature indicating that if you disturb oxygen levels in the eye--including after cataract surgery--the risk of developing glaucoma increases."

John says that mutations in the TDRD7 gene could cause a double jeopardy for childhood glaucoma. “First, they cause cataract, and cataract extraction may raise oxidative stress in the ocular drainage tissues. Second, they impair the formation of protective stress granules in response to oxidative stress."

In an indication of the paper's landmark status, *Science* is publishing the report together with a Perspective article on the study's implications for RNA granule research. Lachke, now an instructor in medicine, comments, "This is a good example of a 21st century collaboration, with major contributions by multiple groups, including basic and clinical researchers across multiple continents."

Jackson Research Scientist Richard Smith, M.D., a former eye surgeon now in the John lab, describes pediatric cataracts as "a very difficult problem to deal with" in the clinic. "The surgical techniques have gotten better," he says, "but a lot of these kids get cataracts shortly after birth, a period with substantially increased glaucoma risk following cataract extraction." Smith notes that while pediatric cataracts are relatively rare in the United States (occurring in about one in every 30,000 births), they are a major problem in other parts of the world, notably the Middle East. "In Saudi Arabia about one in 2,500 babies is born with juvenile cataracts," Smith says.

Glaucoma accounts for about 10 percent of all blindness, with about 4 million cases in the United States. The eye disease, which has no cure, is generally associated with raised pressure within the eye, called intraocular pressure, which damages the optic nerve. Earlier this month the John lab reported that they identified early stages of glaucoma in mice, and successfully blocked the disease in some of the mice by targeting some of the molecular events in those early stages.

More information: Mutations in the RNA Granule Component TDRD7 Cause Cataract and Glaucoma. *Science*, March 25, 2011

Provided by Jackson Laboratory