National Institute of Environmental Health Sciences

Superfund Research Program

Research Brief 283

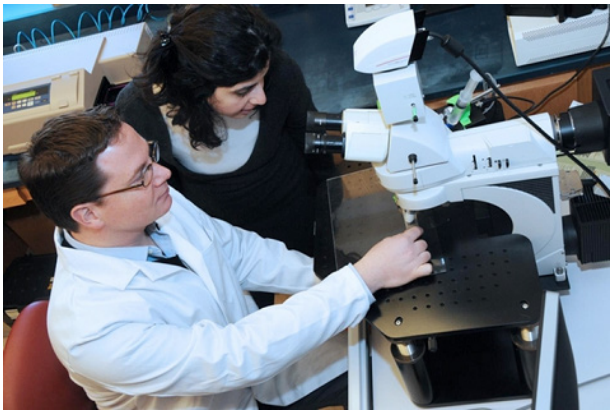
Release Date: 07/11/18

Researchers Identify Compounds that Reduce Abnormal Blood Vessel Growth in the Eye

Scientists have identified key compounds produced when the body metabolizes omega fatty acids that can reduce the severity of age-related macular degeneration (AMD) in mice. By increasing these lipid metabolites and preventing them from degrading, the researchers reduced abnormal blood vessel growth, in part by regulating the movement of inflammatory immune cells into the retina.

AMD is the most common cause of blindness among the elderly in the developed world. In patients with advanced AMD, abnormal blood vessels start to develop under the light-sensing layer of the eye in a process known as choroidal neovascularization (CNV). These cases, known as neovascular AMD, account for 10 to 15 percent of AMD cases. The blood vessels develop abruptly and rapidly lead to substantial vision loss.

To explore the effects of fatty acid-derived metabolites on CNV, researchers led by Kip Connor, Ph.D., an assistant professor at Harvard Medical School, used molecular tools developed at the University of California (UC) Davis Superfund Research Program (SRP) Center and genetic tools developed by the Environmental Cardiopulmonary Disease Group at NIEHS.



Study authors Connor and Lama Mulki, M.D., use a microscope in the Connor lab at Harvard Medical School. (Photo courtesy of Kip Connor)

Identifying the Role of Lipid Metabolites

In the body, omega-3 and omega-6 fatty acids are metabolized by a family of enzymes known as cytochrome P450 (CYP). They are then further degraded by the enzyme soluble epoxide hydrolase (sEH), which was originally discovered by UC Davis SRP Center Director Bruce Hammock, Ph.D. Hammock and his team have developed molecular tools to inhibit sEH to learn more about the intermediate metabolites.

In this study, Connor and his team collaborated with Hammock and NIEHS investigator Darryl Zeldin, M.D., to investigate the role of these metabolites on CNV. Using mice with altered CYP pathways designed to increase or decrease the levels of sEH, the researchers identified intermediate compounds responsible for reducing CNV. Specifically, they isolated and characterized two fatty acid-derived metabolites from the CYP pathway: 17,18-epoxyeicosatetraenoic acid (EEQ) and 19,20-epoxydocosapentaenoic acid (EDP).

They found that inhibiting sEH in mice led to increased levels of EDP and EEQ and protected mice prone to AMD from developing abnormal blood vessels. When they promoted degradation of these intermediate lipid metabolites by increasing sEH, CNV increased.

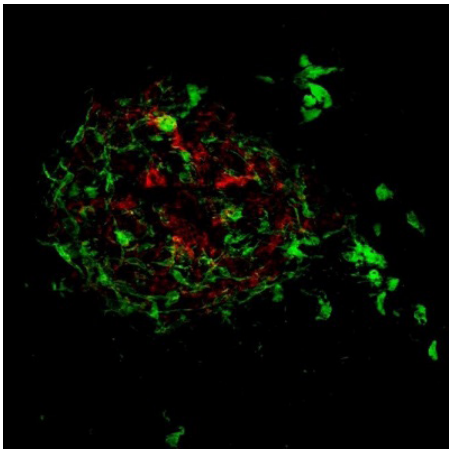
Links to the Immune System

The researchers found that these lipid metabolites work in part by regulating the recruitment of immune cells to CNV lesions.

CNV progression in AMD requires recruitment of inflammatory immune cells from circulating blood into the retina. In this study, the researchers demonstrated that EEQ and EDP reduce the ability of inflammatory immune cells in the blood to attach to tissues in the retina. This is because EEQ and EDP molecules reduce the expression of small molecules on immune cells that have the job of adhering to tissues.

Various environmental factors, including chemical exposures, may contribute to chronic inflammation, which can lead to a variety of diseases and conditions. According to the authors, the research demonstrates that these lipid metabolites can regulate inflammatory immune cells, showing promising therapeutic potential for AMD, as well as other major conditions that involve inflammation, such as cardiovascular disease and cancer.

"Identifying mechanisms that regulate abnormal blood vessel growth in the eye could open up a range of possibilities for new research and treatments for AMD," Connor said.



A CNV lesion in the retina with associated blood vessels, in red, and immune cells, in green. (Photo courtesy of Kip Connor)

A Collaborative Effort

The study, based in Connor's laboratory at Harvard, builds on work led by Hammock and Zeldin to study biologically active lipids. The collaboration spawned from a chance meeting between Hammock and Eiichi Hasegawa, Ph.D., a doctoral fellow in the Connor lab at the time and the first author on the paper. The researchers discussed potential applications of sEH inhibitors in AMD, which has led to a long-term collaboration between the two laboratories.

Hammock continues to study how blocking sEH can reduce inflammation and inflammatory pain related to a number of diseases, including Parkinson's disease, cardiac fibrosis, and depression. Hammock is CEO of the Davis-based company EicOsis, which is developing sEH inhibitors that soon will enter human clinical trials supported by the Blueprint Program of the National Institute of Neurological Disorders and Stroke.

In addition to partial support from the UC Davis SRP Center, this study was funded by fellowship grants and research support from the Harvard Department of Ophthalmology, the Massachusetts Eye and Ear Infirmary, the Massachusetts Lions Eye Research Fund, the BrightFocus Foundation, Research to Prevent Blindness, the Japan Society for the Promotion of Science, the Intramural Program of the NIEHS, and NIEHS grants R01ES002710, K99ES024806, and R00ES024806.

For more information, contact:

Bruce D. Hammock, Ph.D.
University of California, Davis
Department of Entomology
90 Briggs Hall
Davis, California 95616
Phone: 530-752-7519
Email: bdhammock@ucdavis.edu

To learn more about this research, please refer to the following source:

Hasegawa E, Inafuku S, Mulki L, Okunuki Y, Yanai R, Smith KE, Kim CB, Klokman G, Bielenberg DR, Puli N, Falck JR, Husain D, Miller JW, Edin ML, Zeldin DC, Lee KSS, Hammock BD, Schunck WH, Connor KM. 2017. Cytochrome P450 monooxygenase lipid metabolites are significant second messengers in the resolution of choroidal neovascularization. Proc Natl Acad Sci U S A 114(36):E7545-E7553. doi: 10.1073/pnas.1620898114 PMID: 28827330