Retinal cells may have the potential to protect themselves from diabetic retinopathy

Cells within retinal blood vessels are endowed with a previously unappreciated ability to acquire resistance against the damaging effects of hyperglycemia in patients with diabetes mellitus, researchers report in The American Journal of Pathology

Philadelphia, November 29, 2022 – About one third of patients with diabetes mellitus (DM) develop diabetic retinopathy (DR), a leading cause of blindness in working-age individuals. DR typically develops after many years of DM, and some patients do not develop DR for more than 50 years. New research suggests that an endogenous system that protects human retinal endothelial cells from harmful effects of the hyperglycemia (an excess of blood sugar) may be responsible for the delayed onset of DR. Furthermore, degradation of this protective system over time may set the stage for development of DR. The new study appears in The American Journal of Pathology.

“The prevailing understanding of what causes DR predicts that it will develop soon after the onset of DM,” explained lead investigator Andrius Kazlauskas, PhD, Departments of Ophthalmology and Visual Sciences and Physiology and Biophysics, University of Illinois at Chicago, Chicago, IL, USA. “Yet this is not the case. Although the long delay from the onset of DM to the development of DR is a well-known clinical phenomenon, there is relatively little effort to investigate the underlying reason for this delay. Uncovering this information constitutes an exciting opportunity to improve current approaches to prevent DM from progressing to DR.”

Exposing cultured cells, such as vascular endothelial cells, to high glucose is a common in vitro model of DR. The investigators cultured human retinal endothelial cells in either normal glucose or high glucose-containing media. Unexpectedly, they found that prolonged exposure to high glucose was beneficial, not detrimental. After one day,
the health of the cells declined, but as the duration of exposure was prolonged, the cells recovered and acquired resistance to DM-related damage such as inflammation and death.

The investigators found that the adaptation was associated with improved mitochondria functionality. Mitophagy is the process in which cells remove damaged mitochondria, and disruption of this intrinsic quality control system is associated with many diseases. Though initially compromised, mitochondrial functionality was improved after 10 days of exposure to high glucose, with increased clearance of damaged mitochondria. Interfering with the mitochondrial dynamics compromised the cells’ ability to endure high glucose. Susceptibility to cell death increased, and responsiveness of vascular endothelial growth factor deteriorated.

Dr. Kazlauskas said these observations indicate the existence of an endogenous system that protects human retinal endothelial cells from the deleterious effects of hyperglycemia. “The compelling role of mitochondrial dysfunction in the development of DR supports our central concept of a hyperglycemia-induced mitochondrial adaptation (HIMA) system, the purpose of which is to preserve the functionality of mitochondria. We posit that the loss of HIMA sets the stage for advancing to DR.”

An important component of the HIMA concept is that improving the functionality of a subset of retinal cells will be beneficial for the whole retina. Previous research has found even a small reduction in degree or type of insult to the retina can protect animals that have DM from developing DR. Together these discoveries suggest that the development of DR involves a relatively small shift in the balance between exogenous insults and the endogenous systems that prevent DM-driven damage and drivers of pathogenesis.

Dr. Kazlauskas observed that the increasing incidence of DM, and consequently of DR, around the world exacerbates the need for effective approaches to protect patients from this serious complication. “Does HIMA exist in vivo, does it protect patients from DR, and is its demise a prerequisite for progression to DR? Our ongoing research is focused on answering these open questions,” he concluded.
Notes for editors

The article is openly available at https://ajp.amjpathol.org/article/S0002-9440(22)00258-9/fulltext.

The study was funded by grants from the Juvenile Diabetes Research Foundation, Illinois Society to Prevent Blindness, National Institutes of Health grant EY031350, and a Research to Prevent Blindness Foundation unrestricted grant.

Full text of the article is also available to credentialed journalists upon request. Contact Eileen Leahy at +1 732 238 3628 or ajpmedia@elsevier.com to request a PDF of the article. To request an interview with the authors please contact Andrius Kazlauskas, PhD, at ak20@uic.edu.

About The American Journal of Pathology
The American Journal of Pathology, official journal of the American Society for Investigative Pathology, published by Elsevier, seeks high-quality original research reports, reviews, and commentaries related to the molecular and cellular basis of disease. The editors will consider basic, translational, and clinical investigations that directly address mechanisms of pathogenesis or provide a foundation for future mechanistic inquiries. Examples of such foundational investigations include data mining, identification of biomarkers, molecular pathology, and discovery research. High priority is given to studies of human disease and relevant experimental models using molecular, cellular, and organismal approaches. https://ajp.amjpathol.org

About Elsevier
As a global leader in information and analytics, Elsevier helps researchers and healthcare professionals advance science and improve health outcomes for the benefit of society. We do this by facilitating insights and critical decision-making for customers across the global research and health ecosystems.

In everything we publish, we uphold the highest standards of quality and integrity. We bring that same rigor to our information analytics solutions for researchers, health professionals, institutions and funders.

Elsevier employs 8,700 people worldwide. We have supported the work of our research and health partners for more than 140 years. Growing from our roots in publishing, we offer knowledge and valuable analytics that help our users make breakthroughs and drive societal progress. Digital solutions such as ScienceDirect, Scopus, SciVal, ClinicalKey and Sherpath support strategic research management, R&D performance, clinical decision support, and health education. Researchers and healthcare professionals rely on our over 2,700 digitized journals, including The Lancet and Cell; our over 43,000 eBook titles; and our iconic reference works, such as Gray’s Anatomy. With the Elsevier Foundation and our external Inclusion & Diversity Advisory Board, we work in partnership with diverse stakeholders to advance inclusion and diversity in science, research and healthcare in developing countries and around the world.

Elsevier is part of RELX, a global provider of information-based analytics and decision tools for professional and business customers. www.elsevier.com