

Genetic System Offers Option for Studying Role of Retinal Müller Cells

The function of VEGF in retinal neovascularization is widely acknowledged, but the role of retinal Müller cells in neovascularization has not been well investigated.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

Retinal neovascularization and retinal vascular leakage are common pathogenic changes and major causes of vision loss in diabetic patients. It is well known that overexpression of vascular endothelial growth factor (VEGF or VEGF-A) in the retina of a patient with diabetes plays a pivotal role in these pathogenic changes.

“It has been suggested that the retinal Müller cell is the major source of VEGF in [the retina of patients with diabetes] and thus, the major player in diabetic retinopathy [DR],” reported Yun Z. Le, PhD, at the American Diabetes Association’s 67th Scientific Sessions in Chicago.¹ “The significance of Müller cell-produced VEGF in DR, however, has not been well investigated.”

Dr. Le said in an e-mail to *Retina Today* that the role of retinal Müller cells in neovascularization was speculated in 1995,² however there have not been many studies that deal with the in vivo mechanisms of these cells in DR. “This is really important to the understanding of the mechanisms and the design of effective treatment for the disease.”

To better elucidate the role of the retinal Müller cells in DR, Dr. Le and his team disrupted Müller cell-produced VEGF in mice using tetracycline-inducible system and Cre-lox technology. According to the National Institutes of Health,³ Cre-lox technology involves site-specific recombination of DNA using the *cre* gene and lox sites. Its usefulness in basic medical research is widely recognized. Cre-lox site-directed recombination has shown great utility in improving existing gene knockout technology, particularly when used in mouse models of conditional gene expression.

Dr. Le and colleagues then investigated the effect of

VEGF disruption on retinal neovascularization and vascular leakage.

The investigators generated inducible Müller cell-specific VEGF knockout mice by mating the floxed VEGF mice with the tetracycline-inducible Müller cell-specific Cre mice developed in their laboratories. The conditional VEGF knockout mice were subjected to an oxygen inducible retinopathy (OIR) model, he said. VEGF expression, retinal neovascularization, and vascular leakage in the OIR model-treated conditional VEGF knockout mice were analyzed with immunohistochemistry, fluorescein angiography, and quantification of neovascular nuclei.

VEGF expression was reduced significantly in the conditional VEGF knockout mice, Dr. Le said. Inducible disruption of VEGF in the retinal Müller cells caused reduced neovascularization and vascular leakage in the OIR model.

“Our study demonstrates unequivocally that the retinal Müller cell-produced VEGF plays an important role in retinal neovascularization,” Dr. Le and his colleagues concluded. “Our study provides a genetic system to study the cellular mechanisms that regulate retinal neovascularization. These studies are ongoing.” ■

Yun Z. Le, PhD, is Assistant Professor of Medicine and Adjunct Assistant Professor of Cell Biology, Department of Medicine/Endocrinology, University of Oklahoma Health Sciences Center. He may be reached at Yun-Le@ouhsc.edu.

1. Le YZ, Zheng W, Chen Y, et al. Role of the retinal muller cells in retinal neovascularization. Presented at the American Diabetes Association’s 67th Scientific Sessions. June 22-26, 2007.
2. Pierce EA, Avery RL, Foley ED, et al. Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal vascularization. *Proc Natl Acad Sci USA* 1995;92:905-909.
3. NIH news release. NIH, Jackson Laboratory and DuPont Pharmaceuticals Sign Cre-Lox Technology Use Agreement. Available at: www.nih.gov/news/pr/aug98/od-21.htm. Accessed Aug. 29, 2007.