第 48 卷 第 7 期
2021 年 7 月

湖南大学学报（自然科学版）
Journal of Hunan University（Natural Sciences）

Vol. 48. No. 7.
July 2021

Open Access Article

Investigation of Anti Receptor Advanced Glycation End Product Effect in Pericyte Loss Prevention in Diabetic Retinopathy

Ramzi Amin[1], Rachmat Hidayat[2*], Ria Mutiara[1]

[1] Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

[2] Department of Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

Abstract: Diabetic retinopathy is a microvascular complication that is found due to the condition of diabetes mellitus. This study was aimed to investigate the effect of anti receptor advanced glycation end products on survival pericytes by assessing apoptotic activity and the number of pericytes. This research is an in vivo study that used Sprague-Dawley rats as a study object. The rats were grouped into three groups, group 1 was a control group without induced diabetes, group 2 was rats with induced diabetes, and group 3 was diabetes-induced rats who received anti receptor advanced glycation end products injection. Advanced glycation end-products accumulation was evaluated by the immunohistochemistry method. Apoptotic cells are detected by conjugated streptavidin peroxidase in retinal vascular digests. The diabetic rats showed a 32% increase in body weight than the control group from the metabolic parameter. While anti receptor advanced glycation end group only gained weight 28% higher than the standard group. The immunohistochemistry examination showed that the accumulation of advanced glycation end products was found in the retinal vessels and inner neural retina in the diabetic retinopathy group. In conclusion, anti receptor advanced glycation end products administration can prevent pericyte cell loss in retinal vessels via inhibition of apoptosis and oxidative stress due to inhibition of advanced glycation end products and their receptor interactions in pericyte cells.

Keywords: anti receptor advanced glycation end, pericyte cell, retinal vessel, diabetic retinopathy, in vivo study.

抗受体高级糖化终产物在预防糖尿病视网膜病变周细胞丢失中的作用研究

摘要：糖尿病视网膜病变是一种由于糖尿病的状况而发现的微血管并发症。本研究旨在通过评估细胞凋亡活性和周细胞数量来研究抗受体晚期糖基化终产物对存活周细胞的影响。本研究是一项以斯普拉格-道利大鼠为研究对象的体内研究。将大鼠分为三组，第 1 组为未诱发糖尿病的对照组，第 2 组为诱发糖尿病的大鼠，第 3 组为接受抗受体晚期糖基化终末产物注射的糖尿病诱发大鼠。通过免疫组织化学方法评估晚期糖基化终产物的积累。通过视网膜血管消化物中的结合链霉亲和素过氧化物酶检测凋亡细胞。从代谢参数来看，糖尿病大鼠的体重比对照组增加了 32%。而抗受体晚期糖基化末端组仅比标准组增加了 28%的体重。免疫组化检查显示，糖尿病视网膜病变组视网膜血管和视网膜内层有晚期糖基化终产物的积累。总之，由于晚期糖基化终产物及其受体相互作用在周细胞细胞中的抑制，抗受体晚期糖基化终产物给药可以通过抑制细胞凋亡和氧化应激来防止视网膜血管中周细胞细胞丢失。

关键词：抗受体晚期糖基化末端、周细胞、视网膜血管、糖尿病视网膜病变、体内研究。

Received: April 20, 2021 / Revised: May 19, 2021 / Accepted: June 23, 2021 / Published: July 31, 2021

About the authors: Ramzi Amin,Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia; Rachmat Hidayat, Department of Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia; Ria Mutiara, Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

Corresponding author Rachmat Hidayat, dr.rachmat.hidayat@gmail.com

1. Introduction

Diabetic retinopathy (DR) is a microvascular complication that is found due to the condition of diabetes mellitus (DM) [1]. This complication is one of the causes of blindness that is quite often encountered. This complication is found in almost all type-1-DM patients and about 60% of type 2 DM. Many studies have stated that the process of microvascular complications has taken place since the onset of DM [1], [2]. Based on the study in Karachi, Pakistan, the incidence of retinopathy in diabetes mellitus was about 20% at the initial diagnosis [3], [4]. The Gutenberg Health Study (GHS) shows that as many as 8.2% of the pre-DM population in Germany experience diabetic retinopathy type non-proliferative diabetic retinopathy [5]. It shows that the diabetic retinopathy process is not a continuous process that must take a long time. Even though in the pre-DM stage, the pathophysiology of retinopathy could progress to be more severe stage [5].

The initial stage of non-proliferative diabetic retinopathy is characterized by the loss of pericyte from retinal capillaries, followed by the formation of acellular capillaries and microaneurysms [6]. These conditions cause changes in the permeability of retinal endothelial cells and thinning of the capillary basement membrane, damaging the irreversible capillaries. If this damage continues, it will cause a proliferative phase of diabetic retinopathy, characterized by neovascularization, leakage of capillaries, vitreous hemorrhage, retinal detachment, and vision loss [1], [7].

Increased glucose levels in the blood and tissues cause upregulation of modification of proteins, fats, and nucleic acids after an interaction with aldose occur, forming AGE (advanced glycation end product) [8]. AGE will then bind to the cellular receptor known as RAGE (receptor advanced glycation end product). RAGE is a superfamily protein immunoglobulin located in various cells, such as macrophages, monocytes, endothelial cells, smooth muscle cells, and hepatocytes [8], [9]. RAGE is found in vascular endothelial cells, pericyte, microglial, and retinal pigmented epithelium (RPE) cells in the eyeball. The expression is upregulated with increasing AGE due to hyperglycemia [10]. AGE bonding with RAGE will induce various pathways. Activation of oxidative stress impacts AGE and RAGE bonds, where oxidants will cause the activation of death receptors in the pericyte, activating apoptosis and irreversible pericyte damage [9], [10]. Pericyte is a perivascular cell that acts as a mesenchymal cell and is located in the basal lamina microvessels, where the pericyte plays a role in maintaining microvascular integrity and homeostasis [11]. These facts show that the pericyte's role is critical in maintaining the integrity and homeostasis of retinal vessels.

RAGE inhibition is one modality that can be developed to prevent further damage from the pericyte and is believed to prevent the progression of diabetic retinopathy. Inhibition of AGE and RAGE bonds will cause inhibition of oxidative stress. This inhibition will cause a decrease in the number of oxidants, preventing pericyte death. This condition shows the potential of anti-RAGE as a promising therapeutic modality to be developed to prevent the progression of microvascular damage in diabetic retinopathy. This study is the first research conducted to evaluate the potential of Anti RAGE on survival pericyte by assessing apoptotic activity and the number of pericyte/mm^2, besides measuring HbA1c, blood glucose, body weight, and AGEs levels to assess the characteristics and standardization of hyperglycemia conditions.

2. Methods/Material

2.1. Ethical Approval

The ethical committee approved this study of the Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia with approval No. 399/kptfkunsri-rsmh/2020.

2.2. Animal Studies

This study used rats (Rattus norvegicus) Sprague-Dawley strain obtained from Eureka Research Laboratory, Palembang, Indonesia. The rats' age was 10 weeks old, supplemented by a health certificate from the Veterinary Department in Palembang, Indonesia.

The rats were grouped into three groups (each group consists of ten rats). Group 1 was normal rats without induced DM, group 2 was rats with induced DM, and group 3 was rats with induced DM and received Anti RAGE injection. For the induction of diabetes mellitus, a rat was injected intraperitoneally with streptozotocin (55 mg/kg BW) dissolved in 0.05 M citrate buffer. The control group performed intraperitoneal injection with vehicle alone. Rats were determined to have diabetes mellitus when blood glucose level $>$ 250 mg/dL. Subcutaneous administration of five units of isophane insulin is given to maintain blood glucose levels around 300 mg/dL three times a week. All rats are given free access to food and drinking water and light-dark cycle, for 14 hours getting daylight and 10 hours getting dark light, the temperature is maintained at 24-25°C. Diabetes mellitus status was assessed by monitoring blood glucose level, body weight, and HbA1c using Roche Diabetes Care GmbH Company tools.

Rats' organ evacuation was done 24 weeks after the rats had hyperglycemia, with first anesthetic injection with intraperitoneal pentobarbital sodium 30 mg/kg BW and enucleated right eyeball, continued fixation in neutralized buffer formalin 10% for 24 hours, and embedded in the embedded 10 mg neutralized buffer

paraffin. After the right eye is evacuated, the left eyeball is resentable and cut into three sectors centered on the optical disc. Then the trypsin-digested vessel process is carried out.

2.3. Anti RAGE Administration

To study the effect of RAGE inhibition, anti-RAGE antibody, a monoclonal antibody specific for rats (developed by Abcam public limited company). Anti RAGE 50 ug was dissolved in 10 µL sterilized phosphate-buffered saline (PBS) (developed by Biogear company), then anti-RAGE was injected intravitreally at weeks 6, 12, and 18 after the onset of hyperglycemia. The control group was given vehicle injection alone, 10 µL sterilized PBS.

2.4. AGEs Level Examination

Examination of AGEs levels in the vitreous fluid was analyzed using the ELISA (enzyme-linked immunosorbent assay) technique (developed by Abcam public limited company), carried out based on manual instruction. An immunohistochemistry method is used to evaluate the accumulation of AGEs in the retina, using antibodies, anti-AGEs (developed by Abcam public limited company). For AGEs detection, incubated with LSAB kit (developed by Dako North America Inc.) and visualized with 3,3'-diaminobenzidine tetrahydrochloride.

2.5. Trypsin-Digested Vessel

Retinal samples were put into 10% formalin for two days. Furthermore, the retina was incubated with trypsin 3% in sodium phosphate buffer containing 0.1 M sodium fluoride for 60 minutes. Isolation of vessels is done by gentle rinsing in distilled water. Next, the mounting process was done to vascular specimens on a slide.

2.6. Immunofluorescence Staining of NG2

Trypsin digests were then stained immunofluorescence by first incubating slides with rat anti neuron glial-2 (NG2) antibody (developed by Abcam public limited company) for 1 hour. The slides were then incubated with fluorescein isothiocyanate (FITC) conjugated goat anti-rat antibody (developed by Abcam public limited company). NG2 expression shows the pericyte quantity, where five selected fields are used to calculate cell expression per mm^2.

2.7. Apoptosis Examination

According to the guidelines in the manufacturer's instructions, a TUNEL assay was used to assess the retinal vascular cell apoptosis kit (DeadEnd apoptosis detection system, developed by Promega Corporation). Apoptotic cells are detected by conjugated streptavidin peroxidase in retinal vascular digests.

2.8. Statistical Analyses

All of the included data in this study were analyzed using SPSS software (v. 25.0 for Windows, SPSS Inc, Chicago, Illinois). Data analysis was performed with student's t-test and one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons.

3. Results

3.1. Metabolic and Physical Parameters

At 34 weeks, all three groups of rats showed different hyperglycemic parameters. The DR group (group 2) showed a 32% increase in body weight compared to the average group weight. While the anti-RAGE group only gained weight 28% higher than the standard group. The DR group showed an increase in blood glucose 365% higher than the average group blood glucose. In comparison, the Anti-RAGE group only experienced a blood glucose increase of 248% higher than the average group blood glucose. Regarding the HbA1c level, the DR group showed an increase in HbA1c levels by 125% compared to the HbA1c levels in the standard group, while the Anti RAGE group showed an increase in HbA1c levels by 100% standard group (table 1). These results indicate the potential of Anti RAGE in reducing worsening hyperglycemia metabolic parameters.

3.2. Expression of AGEs in Retinal Tissue

AGEs expression showed a significant increase in the DR group compared to the standard group. The AGEs protein expression in the DR group was 40% higher than the standard group, while in the anti-RAGE group, the AGEs expression was almost the same as the standard group. On immunohistochemistry, examination showed that the accumulation of AGEs was found in the retinal vessels and inner neural retina in the DR group. This condition showed that the accumulation of AGEs in the serum caused deposits of AGEs in the retinal tissue (Table 2). Giving anti-RAGE can reduce the expression of AGEs in the retinal vessel or the inner neural retina.

3.3. Pericytecell NG2 Expression

Quantitative analysis was performed to calculate the density of NG2 protein expression in capillaries. Table 3 shows that the DR group had lower pericyte cell density than the standard group and anti-RAGE group. The provision of Anti-RAGE can maintain the survival of capillary pericyte cells.

3.4. Apoptosis Assay for Pericyte Cell

Apoptosis is a cell death process that is carried out in a structured and programmed manner. The pericyte loss found in Table 3 is then explored in relation to the

pathways mechanism of pericyte loss. Quantification analysis was performed by measuring the number of positive cells per mm^2 of the capillary area. Table 4 shows that the number of positive TUNEL cells in the DR group is much higher than the standard and Anti RAGE groups. It shows that the DR group's apoptotic activity was higher than in the standard and Anti RAGE groups.

Table 1 Metabolic parameters (All data were expressed as mean $\pm SE$; *p<0,05 VS Normal; #p<0,05 VS DR)

	Normal	DR	Anti-RAGE
Bodyweight (g)	311,3 ± 14,9	410,5±28,7 *	398,3±25,6 *
Blood glucose (mg/dL)	98,8±3,8	456,7±23,4 *	342,3±22,3 * #
HbA1c (%)	3,5±0,1	7,89±0,4 *	7,02±0,3 *

Table 2 Effect of anti RAGE on the accumulation of AGE (Level of AGEs in retinal tissue by ELISA assay. The level of AGEs represents Mean ± SE. * p <0.05 VS Normal. #p <0.05 versus DR)

	Normal	DR	Anti RAGE
AGEs level (mg/mL)	0,5 ±0,01	0,7 ±0,02 *	0,48±0,02#

Table 3 Anti-RAGE effect on histopathological changes (The number of cell pericyte was determined by counting the number of NG2 positive cells per mm2. * p <0.05 versus normal. #p <0.05 versus DR.)

	Normal	DR	Anti RAGE
No. pericyte cell/mm^2	2115,3± 26,5	1765,7±12,8 *	2005,3±36,7#

Table 4 Effect of anti RAGE on apoptosis of retinal pericytes (Quantitative analysis of TUNEL positive cells in trypsin-digested retinal vessels. * p <0.05 versus normal. #p <0.05 versus DR)

	Normal	DR	Anti RAGE
No. TUNEL positivecell/mm^2	3,7± 0,1	12,3± 0,9 *	4,7± 0,2#

4. Discussion

RAGE inhibition is a breakthrough therapy to reduce the progression of diabetic retinopathy [12]. RAGE is receptor-activated in thepresenceofAGEs. These receptors are found in almost all body cells, including pericyte cells, endothelial cells, microglia, and retinal pigmented epithelium [10], [12]. Hyperglycemia condition causes an increase in the formation of AGEs. The AGE/RAGE interaction causes an increase in the production of reactive oxygen species (ROS). ROS causes the activation of death receptors in retinal pericytes, which results in caspase activation and causes apoptosis pericytes [13], [14]. RAGE inhibition by anti-RAGE causes no AGE/RAGE interaction. Of course, the absence of ligand-receptor interactions does not cause various pathological cascade pathways, including the process of apoptosis. This study shows a significant result that the administration of Anti-RAGE can inhibit the oxidative stress process, inhibit the process of apoptosis, and ultimately prevent pericyte loss [12].

This study also showed exciting results, which found the effectiveness of Anti RAGE in reducing the accumulation of AGEs in retinal tissue. The downregulation of RAGE causes this due to decreased accumulation of AGEs. The higher the accumulation of AGEs, causing an increase or upregulation of RAGE, the opposite applies [15]. The competition between AGEs and Anti RAGE in occupying RAGE receptors causes no accumulation of AGEs in retinal tissue. AGEs that fail to accumulate in tissues will prevent oxidative stress processes in various body cells, not only in retinal tissue but also in pancreatic beta cells. Decreased accumulation of AGEs in pancreatic beta cells will inhibit apoptosis and further damage from pancreatic beta cells [15], [16], [17]. Survival of pancreatic beta cells will lead to the optimization of insulin production, which is undoubtedly very helpful in blood glucose homeostasis. This study shows that Anti RAGE administration can reduce blood glucose and HbA1c compared to the DR group.

Destruction of pericyte cells in the retinal is caused by the acellular capillaries' condition, a condition in which the loss of pericyte cells from the retinal vessels is found [11]. The loss of pericyte cells from the retinal vessel causes leaking or leakage of the retinal vessel, which continues on ischemia and neovascularization of the retina, known as proliferative diabetic retinopathy, which is an advanced phase of diabetic retinopathy before blindness occurs [10], [12]. Giving anti-RAGE can inhibit pericyte loss in the retinal vessel; of course, it has a good effect on preventing damage to pericyte cells and preventing diabetic retinopathy progression.

5. Conclusion

Anti RAGE administration effectively prevented pericyte cell loss in retinal vessels via inhibition of apoptosis and oxidative stress due to inhibition of AGEs and RAGE interactions in pericyte cells.

References

[1] WANG W., & LO A. Diabetic retinopathy: Pathophysiology and treatments. *International Journal of Molecular Sciences*, 2018, 19(6): 1816. https://dx.doi.org/10.3390/ijms19061816

[2] MADONNA R., BALISTRERI C. R., GENG Y.-J., and RAFFAELE D. C. Diabetic microangiopathy: Pathogenetic insights and novel therapeutic approaches. *Vascular Pharmacology*, 2017, 90: 1-7. https://doi.org/10.1016/j.vph.2017.01.004

[3] FAWWAD A., MUSTAFA N., BIN ZAFAR A., and KHALID M. Incidence of microvascular complications of type 2 diabetes: A 12 year longitudinal study from Karachi-Pakistan. *Pakistan Journal of Medical Sciences*, 2018, 34: 1058-1063. https://dx.doi.org/10.12669/pjms.345.15224

[4] BUTT A., MUSTAFA N., FAWWAD A., ASKARI S., HAQUE M. S., TAHIR B., and BASIT A. Relationship between diabetic retinopathy and diabetic nephropathy; A longitudinal follow up study from a tertiary care unit of Karachi, Pakistan. *Diabetes and Metabolic Syndrome*, 2020, 14: 1659-1663. https://doi.org/10.1016/j.dsx.2020.08.026

[5] DORCELY B., KATZ K., JAGANNATHAN R., CHIANG S. S., OLUWADARE B., GOLDBERG I. J., and BERGMAN M. Novel biomarkers for prediabetes, diabetes and associated complications. *Diabetes, Metabolic Syndromes and Obesity: Targets and Therapy*, 2017, 10: 345-361. https://doi.org/10.2147/DMSO.S100074

[6] KERN T. S., ANTONETTI D. A., and SMITH L.E.H. Pathophysiology of diabetic retinopathy contribution and limitations of laboratory research. *Ophthalmic Research*, 2019, 62: 196-202. https://doi.org/10.1159/000500026

[7] SINCLAIR S. H., & SCHWARTZ S. S. Diabetic retinopathy - An underdiagnosed and undertreated inflammatory, neuro-vascular complication of diabetes. *Frontiers in Endocrinology*, 2019, 18: 43-48. https://doi.org/10.3389/fendo.2019.00843

[8] GIURDANELLA G., LAZZARA F., CAPORARELLO N., LUPO G., ANFUSO C. D., EANDI C. M., LEGGIO G. M., DRAGO F., BUCOLO C., and SALOMONE S. Sulodexide prevents activation of the PLA2/COX-2/VEGF inflammatory pathway in human retinal endothelial cells by blocking the effect of AGE/RAGE. *Biochemical Pharmacology*, 2017, 142: 145-154. https://doi.org/10.1016/j.bcp.2017.06.130

[9] PRASAD K., & MISHRA M. AGE-RAGE stress, stressors, and antistressors in health and disease. *International Journal Angiology*, 2018, 27: 1-12. https://dx.doi.org/10.1055/s-0037-1613678

[10] XU J., CHEN L.-J., YU J., WANG H.-J., ZHANG F., LIU Q., and WU J. Involvement of advanced glycation end products in the pathogenesis of diabetic retinopathy. *Cellular Physiology and Biochemistry*, 2018, 48: 705-717. https://doi.org/10.1159/000491897

[11] ZHAO H., & CHAPPELL J. C. Microvascular bioengineering: a focus on pericytes. *Journal of Biological Engineering*, 2019, 13: 26. https://dx.doi.org/10.1186/s13036-019-0158-3

[12] SALEH I., MARITSKA Z., PARISA N., and HIDAYAT R. Inhibition of receptor advanced glycation end products as new promising strategy treatment in diabetic retinopathy. *Open Access Macedonian Journal of Medical Sciences*, 2019, 7: 3921-3924. https://doi.org/10.3889/oamjms.2019.759

[13] LI J., CAO Y., LIU W. WANG, Q., QIAN Y., and LU P. Correlations among diabetic microvascular complications: A systematic review and meta-analysis. *Scientific Reports*, 2019, 9: 31-37. https://doi.org/10.1038/s41598-019-40049-z

[14] CHUNG Y. R., CHOI J. A., KOH J. Y., and YOON Y. H. Ursodeoxycholic acid attenuates endoplasmic reticulum stress related retinal pericyte loss in streptozotocin-induced diabetic mice. *Journal of Diabetes Research*, 2017, 2017: 1763292. https://doi.org/10.1155/2017/1763292

[15] KANDA A., DONG Y., NODA K., SAITO W., and ISHIDA S. Advanced glycation end products link inflammatory cues to upregulation of galectin-1 in diabetic retinopathy. *Scientific Reports*, 2017, 7: 16168. https://doi.org/10.1038/s41598-017-16499-8

[16] LAI D.-W., LIN K.-H., SHEU W. H.-H., LEE M.-R., CHEN C.-Y., LEE W.-J., HUNG Y.-W., SHEN C.-C., CHUNG T.-J., LIU S.-H., and SHEU M.-L. TPL2 (Therapeutic targeting tumor progression locus-2)/ATF4 (activating transcription factor-4)/SDF1alpha (chemokine stromal cell-derived factor-alpha) axis suppresses-diabetic retinopathy. *Circulation Research*, 2017, 121: 37-52. https://doi.org/10.1161/circresaha.117.311066

[17] ZHANG Y., WANG L., ZHANG Y., SUN Q., XIA F., WANG R., and LIU L. Nogo-B promotes angiogenesis in proliferative diabetic retinopathy via VEGF/PI3K/Akt pathway in an autocrine manner. *Cellular Physiology and biochemistry*, 2017, 43: 1742-1754. https://doi.org/10.1159/000484061

参考文:

[1] WANG W., 和 LO A. 糖尿病视网膜病变：病理生理学和治疗。国际分子科学杂志，2018, 19(6): 1816. https://dx.doi.org/10.3390/ijms19061816

[2] MADONNA R., BALISTRERI C. R., GENG Y.-J., 和 RAFFAELE D. C. 糖尿病微血管病：发病机制的见解和新的治疗方法。血管药理学，2017, 90: 1-7. https://doi.org/10.1016/j.vph.2017.01.004

[3] FAWWAD A., MUSTAFA N., BIN ZAFAR A., 和 KHALID M. 2 型糖尿病微血管并发症的发生率：来自卡拉奇-巴基斯坦的 12 年纵向研究。巴基斯坦医学杂志，2018, 34: 1058-1063. https://dx.doi.org/10.12669/pjms.345.15224

[4] BUTT A., MUSTAFA N., FAWWAD A., ASKARI S., HAQUE M. S., TAHIR B., 和 BASIT A. 糖尿病视网膜病变与糖尿病肾病的关系；来自巴基斯坦卡拉奇三级保健单位的纵向随访研究。糖尿病和代谢综合征，2020, 14: 1659-1663. https://doi.org/10.1016/j.dsx.2020.08.026

[5] DORCELY B., KATZ K., JAGANNATHAN R., CHIANG S. S., OLUWADARE B., GOLDBERG I. J., 和 BERGMAN M. 糖尿病前期、糖尿病和相关并发症的新型生物标志物。糖尿病、代谢综合征和肥胖：目标和治疗，2017, 10: 345-361. https://doi.org/10.2147/DMSO.S100074

[6] KERN T. S., ANTONETTI D. A., 和 SMITH L.E.H. 糖尿病视网膜病变的病理生理学贡献和实验室研究的局限性。眼科研究，2019, 62: 196-202. https://doi.org/10.1159/000500026

[7] SINCLAIR S. H., 和 SCHWARTZ S. S. 糖尿病视网膜病变 - 一种未被充分诊断和治疗的糖尿病炎症性神经血管并发症。内分泌学前沿，2019, 18: 43-48. https://doi.org/10.3389/fendo.2019.00843

[8] GIURDANELLA G., LAZZARA F., CAPORARELLO N., LUPO G., ANFUSO C. D., EANDI C. M., LEGGIO G.

M., DRAGO F., BUCOLO C., 和 SALOMONE S. 舒洛地昔通过阻断晚期糖基化终产物/受体晚期糖基化终产物的作用，防止人视网膜内皮细胞中磷脂酶一种 2/前列腺素-内过氧化物合酶-2/血管内皮生长因子炎症通路的激活. 生化药理学, 2017, 142: 145-154. https://doi.org/10.1016/j.bcp.2017.06.130
[9] PRASAD K., 和 MISHRA M. 晚期糖基化终产物受体晚期糖基化终产物应激、应激源和健康和疾病中的抗应激源。国际血管学杂志, 2018, 27: 1-12. https://dx.doi.org/10.1055/s-0037-1613678
[10] XU J., CHEN L.-J., YU J., WANG H.-J., ZHANG F., LIU Q., 和 WU J. 晚期糖基化终产物参与糖尿病视网膜病变的发病机制。细胞生理学和生物化学, 2018, 48: 705-717. https://doi.org/10.1159/000491897
[11] ZHAO H., 和 CHAPPELL J. C. 微血管生物工程：关注周细胞。生物工程杂志, 2019, 13: 26. https://dx.doi.org/10.1186/s13036-019-0158-3
[12] SALEH I., MARITSKA Z., PARISA N., 和 HIDAYAT R. 抑制受体晚期糖基化终产物作为治疗糖尿病视网膜病变的新策略。开放存取马其顿医学科学杂志, 2019, 7: 3921-3924. https://doi.org/10.3889/oamjms.2019.759
[13] LI J., CAO Y., LIU W. WANG, Q., QIAN Y., 和 LU P. 糖尿病微血管并发症的相关性：系统评价和荟萃分析。科学报告, 2019, 9: 31-37. https://doi.org/10.1038/s41598-019-40049-z
[14] CHUNG Y. R., CHOI J. A., KOH J. Y., 和 YOON Y. H. 熊去氧胆酸减轻链脲佐菌素诱导的糖尿病小鼠中与内质网应激相关的视网膜周细胞损失。糖尿病研究杂志, 2017, 2017: 1763292. https://doi.org/10.1155/2017/1763292
[15] KANDA A., DONG Y., NODA K., SAITO W., 和 ISHIDA S. 晚期糖基化终产物将炎症线索与糖尿病视网膜病变中半乳糖凝集素-1 的上调联系起来。科学报告, 2017, 7: 16168. https://doi.org/10.1038/s41598-017-16499-8
[16] LAI D.-W., LIN K.-H., SHEU W. H.-H., LEE M.-R., CHEN C.-Y., LEE W.-J., HUNG Y.-W., SHEN C.-C., CHUNG T.-J., LIU S.-H., 和 SHEU M.-L. 靶向肿瘤进展基因座 2/激活转录因子 4/趋化因子基质细胞衍生因子-α 轴的治疗抑制糖尿病视网膜病变. 流通研究, 2017, 121: 37-52. https://doi.org/10.1161/circresaha.117.311066
[17] ZHANG Y., WANG L., ZHANG Y., SUN Q., XIA F., WANG R., 和 LIU L. 网状四通过血管内皮生长因子/磷酸肌醇 3-激酶/蛋白激酶乙通路以自分泌方式促进增殖性糖尿病视网膜病变的血管生成. 细胞生理学和生物化学, 2017, 43: 1742-1754. https://doi.org/10.1159/000484061