REVIEW

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RAGE signaling pathway in inflammatory and vascular pathology of diabetic retinopathy: implications for interventional strategies

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Diabetes is the most common cause of vision deterioration and subsequent vision loss in people worldwide. Long-term hyperglycemia causes structural, neurovascular and metabolic changes in the eye, leading to a progressive loss of light sensitive retinal cells, degeneration of retinal layers and neuroinflammation of optic nerve fibers and, if not treated, leading to the development of diabetic retinopathy and optic nerve damage. Growing evidence indicates that the pathological changes observed in the retina and optic nerve affected by prolonged hyperglycemia might results from several interconnected molecular events and biochemical signaling cascades such as excessive protein glycation, increased oxidative stress and local inflammation triggered by the receptor for advanced glycation end-products (RAGE) along with the upregulation of molecules involved in angiogenesis and cytoskeleton modification including vascular endothelial growth factor (VEGF) and RhoA/Diaph1/profilin1 system. In this review, we focus on the latest advances in uncovering major factors involved in the pathogenesis of diabetic retinopathy and discuss novel, non-invasive treatment options aimed at the cause rather than symptoms of the disease.

Key words: diabetes, retinopathy, receptor for advanced glycation end-products, Diaph1, pathogenesis, treatment

INTRODUCTION

Diabetes and Retina

Diabetic retinopathy

Diabetes mellitus is one of the fastest-growing non-communicable diseases worldwide. According to the International Diabetes Federation, one in ten adults globally live with diabetes (Sun et al., 2022). Chronic, especially uncontrolled, diabetes is associated with both microvascular and macrovascular complications. Among the most affected organs by microvascular pathology are kidneys and retina. The increasing global prevalence of diabetes has been accompanied by a corresponding rise in the incidence of diabetic retinopathy (DR). DR is a neurovascular complication that affects approximately 30–40% of individuals with diabetes, often resulting in vision impairment or its loss (Yau et al., 2012). Currently, the global prevalence of DR stands at approximately 103 million individuals and is projected to rise to 161 million by 2045 (Teo et al., 2021). The most significant non-modifiable risk factor for DR is the duration of diabetes, while the most critical modifiable factor is chronic hyperglycemia (Klein et al., 1989; Scanlon et al., 2013). Additionally, glycemic variability (GV), defined as fluctuations in blood glucose levels, has emerged as a contributor to DR pathogenesis. The role of GV in diabetic complications became

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increasingly evident with the advent of continuous glucose monitoring (CGM) technologies (Hsing et al., 2021; Cai et al., 2023; Zhai et al., 2023).

Improvements in time in range (TIR) are associated with a decreased risk of DR. Beck et al. (2019) demonstrated that each 10-percentage point decrease in TIR increased the adjusted hazard ratio for DR development by 64% (95% CI: 51–78; P<0.001). Both lower TIR and elevated HbA1c levels indicate poor metabolic control and are predictive of increased DR risk (Walicka & Franek, 2024). However, clinicians should note that rapid improvement in glycemic control may paradoxically worsen DR, a phenomenon known as early worsening of DR (EWDR). This underscores the dominant role of glucose metabolism in DR pathogenesis (Feldman-Billard et al., 2018; Vilsbøll et al., 2018; Matuszewski et al., 2021; Buckley et al., 2025).

Neuro-ophthalmic Manifestations in Diabetes Beyond DR

In addition to DR, diabetes can affect the optic nerve, although ocular neuropathies are less common than peripheral neuropathies. Prolonged hyperglycemia leads to structural, neurovascular, and metabolic changes within the eye, resulting in progressive loss of photoreceptor cells, degeneration of retinal layers, and optic nerve neuroinflammation (Lee et al., 2023). Diabetes is associated with both diabetic papillopathy and anterior ischemic optic neuropathy and it is considered a risk factor for several forms of glaucoma (Muayad et al., 2025). Moreover, gestational diabetes has been linked to optic nerve hypoplasia, particularly the superior segmental variant, which may serve as a clinical marker of maternal diabetes (Nelson et al., 1986). If left uncontrolled, diabetes can lead to both DR and optic nerve damage, ultimately resulting in visual impairment or blindness. While these complications were traditionally considered to be purely microvascular, advanced imaging technologies have revealed that inflammation and neurodegeneration also play significant roles (de Lemos et al., 2024). Metabolic dysfunctions associated with diabetes including oxidative stress and dyslipidemia further contribute to retinal tissue damage. These pathogenic insights into DR have facilitated the development of novel therapeutic agents targeting microvascular injury, inflammation, and metabolic dysregulation in DR.

Novel Therapeutic Strategies in DR: Sulodexide and Fenofibrate

Sulodexide

Sulodexide, a glycosaminoglycan with venoactive properties, has been in clinical use for over three decades. It comprises 80% low-molecular-weight heparin and 20% dermatan sulfate (Cosmi et al., 2003; Andreozzi, 2012; Gericke et al., 2021). Initially indicated for thromboembolic disease, venous insufficiency and arterial occlusive disorders, sulodexide has also shown efficacy in treating hard exudates in mild to moderate non-proliferative DR (NPDR) (Song et al., 2015). Its pharmacological actions in the retina include anti-inflammatory, antithrombotic, fibrinolytic, and antioxidant effects. Sulodexide's negative charge stabilizes the retinal vascular endothelium (Broekhuizen et al., 2010; Yin et al., 2017; Dauth et al., 2023, Kaur & Harris, 2023). A multicenter, double-masked, randomized controlled trial (DRESS) involving 130 patients with type 1 and type 2 diabetes demonstrated the efficacy of sulodexide at 50 mg daily for 12 months. The treatment group showed a significantly greater reduction in hard exudate severity compared to placebo (39.0% *vs.* 19.3%; χ^2, P=0.005) (Song et al., 2015). Additional studies indicated improvements in glycocalyx thickness and normalization of retinal vascular permeability (Broekhuizen et al., 2010).

Fenofibrate

Fenofibrate, a fibrate-class lipid-lowering agent, functions as an agonist of peroxisome proliferator-activated receptor-alpha (PPARα). Dyslipidemia is a well-established risk factor for DR progression. A cohort study involving 1,340 patients found that 83% of those with DR had coexisting dyslipidemia (Amutha et al., 2017). Elevated LDL cholesterol levels, in particular, have been implicated in DR pathogenesis (Lee et al., 2018). Fenofibrate's effects include inhibition of inflammation, suppression of VEGF expression under hypoxic conditions, and enhancement of the blood-retina barrier. It also downregulates pro-inflammatory mediators like ICAM-1 and MCP-1, and inhibits transcription factors such as HIF-1 and NF-κB (Chen et al., 2013; Mazzeo et al., 2020; Gallucci et al., 2022). In genetically modified mice lacking PPARα, fenofibrate lost its protective effect, confirming receptor dependency (Chen et al., 2013).

In animal models, fenofibrate reduced retinal vascular permeability by inhibiting COX-2, fibronectin, and collagen IV expression, while promoting tight junction integrity *via* ZO-1 (Trudeau et al., 2011; Roy et al., 2015). Neuroprotective effects have also been demonstrated, including decreased glial activation and reduced apoptosis in retinal ganglion cells (Bogdanov et al., 2015).

Two large clinical trials, FIELD and ACCORD-EYE, further validated fenofibrate's efficacy. The FIELD study (n=9.795) showed a significant reduction in macular edema and need for laser treatment in patients with

existing retinal changes, irrespective of plasma lipid levels (Keech et al., 2007). In the ACCORD-EYE study, fenofibrate slowed DR progression over four years (P=0.006) (ACCORD Study Group et al., 2010). The LENS study (n=1.150) confirmed a 27% reduction in DR progression or need for ophthalmologic intervention in patients with early-stage DR (Henry et al., 2024; Preiss et al., 2024; Silva & Aiello, 2024; Varughese et al., 2025).

RAGE and its extracellular ligands: Amplifiers of pathology in DR

Despite the advances described above, it remains essential to identify molecular targets involved in specific signaling pathways in the pathogenesis of DR, in order to develop more precise interventional strategies. Increasing evidence indicates that pathological changes observed in the retina and optic nerve in diabetes are largely driven by prolonged hyperglycemia, which remains the most important modifiable risk factor. Chronic hyperglycemia can initiate a series of interconnected molecular events and biochemical signaling cascades, including excessive protein glycation resulting in increased oxidative stress, and local inflammation mediated by the receptor for advanced glycation end-products (RAGE). Therefore, a thorough investigation of RAGE-mediated signaling pathways is critical to understanding the development of DR (Zglejc-Waszak et al., 2021; Juranek et al., 2022). RAGE was first identified as a cell surface receptor for advanced glycation end-products (AGEs), which are products of nonenzymatic glycation and oxidation of proteins and lipids (Neeper et al., 1992; Schmidt et al., 1994). These compounds accumulate during physiological aging, as well as in pathological conditions such as diabetes, inflammatory diseases, and neurodegenerative disorders. RAGE belongs to a group of pattern recognition receptors, which are also part of the RhoA signaling cascade. It also functions as a signal transduction receptor, whose activation triggers the release of proinflammatory molecules, oxidative stressors, and cytokines (Schmidt et al., 2000).

Long-term hyperglycemia drives metabolic changes in the retina and optic nerve, leading to increased protein glycation. Increase in protein glycation prompts the activation of endothelial and microglial RAGE and stimulates the production of reactive oxygen species (ROS) and inflammatory responses (Fig. 1). Under normal conditions, RAGE expression in the retina remains low in neuronal, vascular, and epithelial layers.

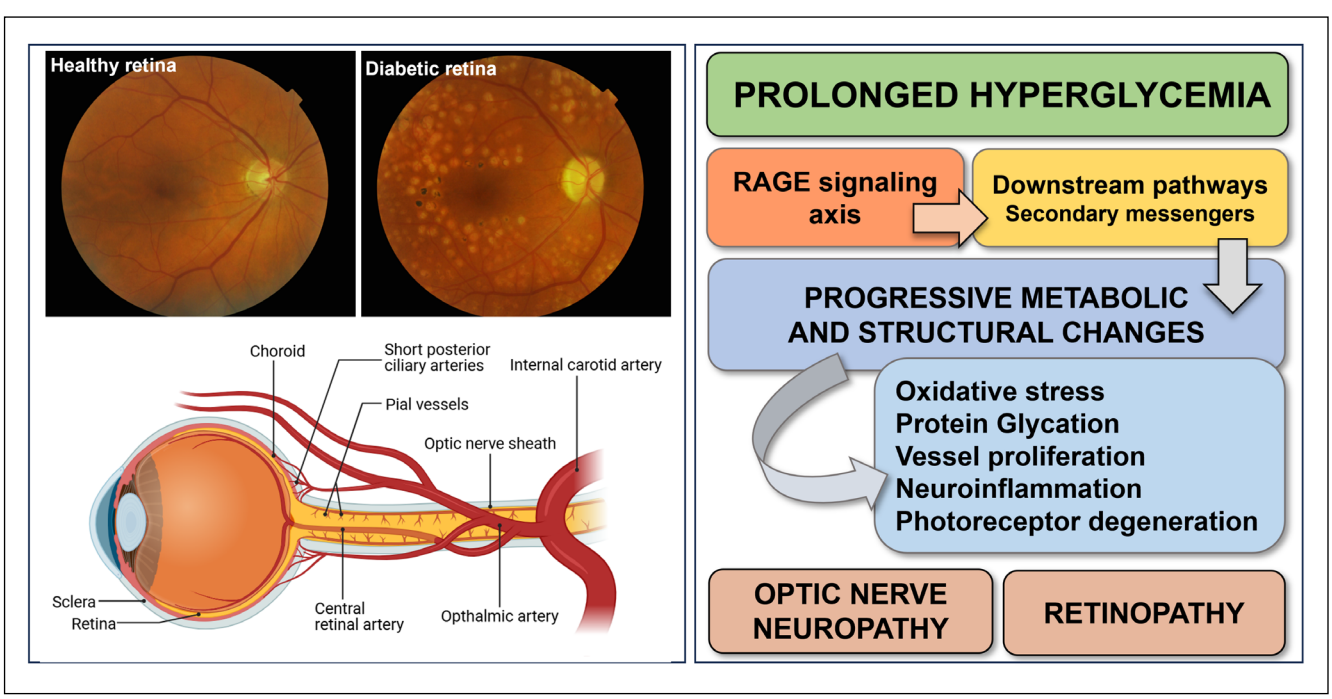

Fig. 1. Diabetic retinopathy pathogenesis – role of RAGE signaling axis. Anatomical and functional changes in retina and optic nerve are among the most common complications of diabetes and a major cause of vision loss in the world. The underlying pathological processes leading to the development of diabetic retinopathy include increased oxidative stress and protein glycation, inflammation, accelerated vessel proliferation and photoreceptor degradation. RAGE signaling axis plays a prominent role in many of these processes, contributing to multiple downstream metabolic pathways involved in diabetic complications. Representative digital scans of healthy and non-healthy retina (nonproliferative diabetic retinopathy). Retina images: eye, optic nerve and surrounding structures created in BioRender. Juranek, J. (2025) https://BioRender.com/l8j6y6p.

However, its expression significantly increases under hyperglycemic conditions and in diabetes (Fan et al., 2021). Studies have shown that deletion of RAGE leads to reduced vascular permeability, leucostasis, and microglial activation in the retina over a six-month period in type 1 diabetic mice. In type 2 diabetic monkeys, RNA sequencing of the retinal pigment epithelium revealed an upregulation of AGE/RAGE signaling, as well as increased activity in complement and inflammatory pathways (Fan et al., 2021) signifying the importance of RAGE in the pathogenesis of diabetic visual impairments. These changes are accompanied by the upregulation of molecules involved in angiogenesis and cytoskeletal modifications, including vascular endothelial growth factor (VEGF) and RhoA/Diaph1/profilin1 system (Fan et al., 2021).

RAGE signaling pathway lead to vascular inflammation, increased permeability of the blood-retinal barrier, endothelial dysfunction, and pathological alterations in both neural and vascular layers of the retina, ultimately resulting in the development of DR (Barile et al., 2005). Interestingly, evidence suggests that Müller cells are particularly vulnerable to hyperglycemia. Most likely, this is in response to the hyperglycemia-induced overproduction of AGEs and their interaction with RAGE activating Müller cells. This overactivity leads to the overexpression of glial fibrillary acidic protein (GFAP), which in turn promotes gliosis (Kida et al., 2021). Studies indicate that RAGE's contribution to DR may be linked to its ability to bind various ligands, thereby activating multiple detrimental signaling pathways. Here, we discuss both AGE and non-AGE, protein ligands of RAGE.

Advanced Glycation End-products (AGEs)

AGEs are critical ligands for RAGE (Xue et al., 2011) formed endogenously under conditions such as hyperglycemia, aging, oxidative stress, and renal failure. Exogenous sources include dietary intake and tobacco products (Cerami et al., 1997). AGEs contribute to both microvascular and macrovascular complications of diabetes, and their interaction with RAGE plays a central role in the development of DR. AGEs comprise a heterogeneous group of compounds, including carboxymethyllysine (CML), carboxyethyllysine (CEL), methylglyoxal-lysine dimer (MOLD), glyoxal-lysine dimer (GOLD), glycolic acid lysine amide (GALA), and pyralline. In diabetic retinas, AGE accumulation has been observed in vascular cells, neurons, and glial cells, which may contribute to retinal dysfunction. AGE/RAGE signaling has been shown to increase NF-κB and VEGF levels, promoting vascular abnormalities.

The presence of AGEs in retinal vessels and neuroglia leads to pericyte damage, an early and critical event in the pathogenesis of DR (Kim et al., 2012). During diabetes, AGEs accumulate in retinal capillary pericytes, which are essential for endothelial cell survival. The destruction of pericytes results in basement membrane thickening, endothelial damage, hyperpermeability, and vasodilation. Activation of AGE–RAGE axis generates ROS in cultured retinal pericytes, increases NF-κB activation, lowers the Bcl-2/Bax ratio, and elevates caspase-3 activity, ultimately leading to pericyte apoptosis and VEGF overproduction (Hammes et al., 2002; Yamagishi et al., 2002; Kim et al., 2012). Recent studies indicate that even low concentrations of AGEs can induce NF-κB expression, promoting neuronal apoptosis and reduced neurite regeneration in cultured retinas (Bikbova et al., 2013). Hyperglycemia also impairs the ability of pericytes to protect against inflammation-induced apoptosis in the retina. Inhibition of AGE/RAGE signaling thus presents a promising therapeutic strategy for preventing the progression of DR.

Liraglutide, a glucagon-like peptide-1 (GLP-1) analog, has demonstrated protective effects against AGEs and preserves retinal function in early-stage DR. Early administration of liraglutide inhibits retinal pericyte migration, reduces microvascular permeability, and supports blood-retinal barrier (BRB) integrity (Lin et al., 2018). Aminoguanidine, an AGE formation inhibitor, has also shown efficacy in animal models by reducing retinal damage, pericyte loss, microaneurysm formation, endothelial proliferation, and AGE accumulation (Hammes et al., 1991). Other AGE blockers, such as pyridoxamine, have been effective in reducing capillary atrophy and extracellular matrix gene expression in diabetic rat retinas (Stitt et al., 2002; Fig. 2).

Carboxymethyllysine (CML) is one of the most abundant AGEs in diabetic patients and binds to RAGE, influencing cellular physiology (Kislinger et al., 1999). Elevated CML levels have been detected in blood of patients with both non-proliferative and proliferative DR. Immunohistochemical studies have shown increased anti-CML antibody staining in the extracellular matrix of diabetic retinas, associated with elevated CD40 expression (Choudhuri et al., 2013). CML is a significant predictor of photoreceptor disruption, particularly in the external limiting membrane (ELM) and ellipsoidal zone, which are associated with reduced visual acuity. Increased serum CML levels also correlate with structural changes in the RPE, suggesting that CML may serve as a biomarker for retinal neurodegeneration and changes in retinal thickness in type 2 diabetes (Hernández et al., 2020).

AGEs like CML are also likely to promote inflammation, a major contributor to diabetic complications,

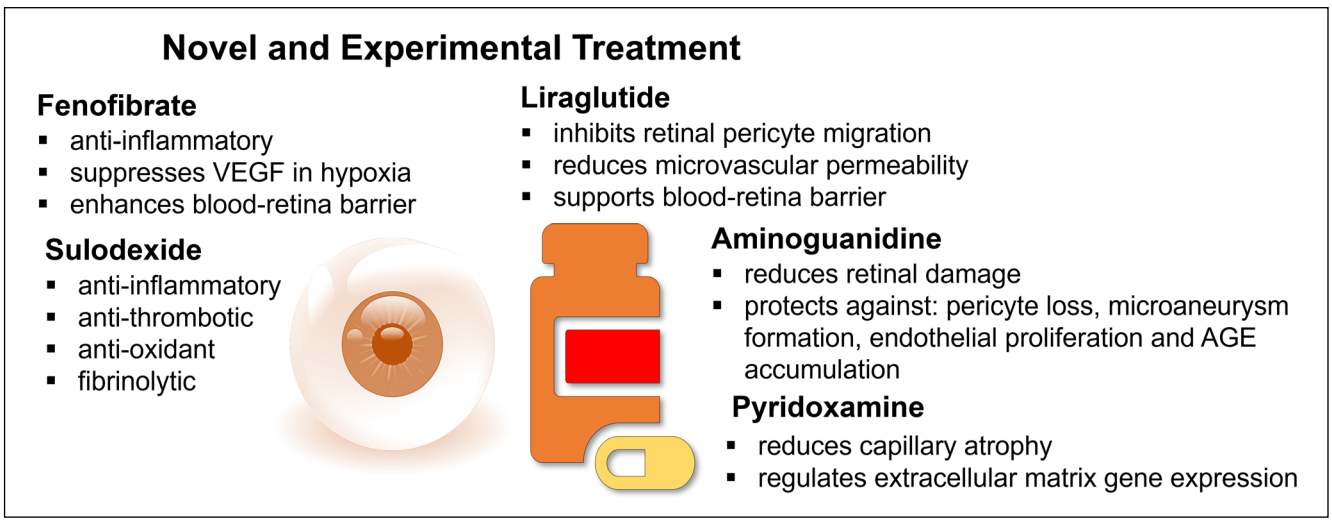

Fig. 2. Novel and experimental treatment in diabetic retinopathy therapy. While fenofibrate and sulodexide have been on the market for some time, their use in DR therapy has been very recent. Both drugs reduce the need for more invasive and expensive treatment making them a very desirable alternative to other more cumbersome and/or expensive options. Liraglutide, aminoguanidine and pyridoxamine are AGE blockers and have been successfully used in treating DR in animal models of the disease. It might be speculated that while still in the experimental phase, these drugs will enter clinical trial soon.

including DR. AGEs increase CD40 expression, which promotes pro-inflammatory responses. AGE-induced signaling upregulates CD40 in endothelial and Müller cells, enhancing ICAM-1 expression and CCL2 production (Portillo et al., 2024). The herb *Trapa bispinosa Roxb.*, known for its antioxidant properties, inhibits CML formation and AGE cross-linking. Systemic administration of *Trapa bispinosa Roxb.* and lutein has been shown to reduce AGE accumulation in retinas of streptozotocin-induced diabetic rats. Improvements in retinal blood flow regulation, decreased GFAP expression in Müller cells, and reduced VEGF levels have also been observed (Hanaguri et al., 2022).

Methylglyoxal (MGO), a reactive AGE precursor formed during glycolysis and pyralline, a Maillard reaction product formed during glucose–protein interaction may accumulate in retina and optic nerve head in chronic hyperglycemia and contribute significantly to diabetic pathology (Amano et al., 2001; Schlotterer et al., 2019). AGE accumulation in optic nerve vessels is also believed to impair microcirculation and contribute to diabetic optic neuropathy. In retinal endothelial cells, MGO induces lysyl oxidase expression *via* RAGE, promoting matrix stiffening and inflammation. MGO also triggers ROS-induced mitochondrial dysfunction, NLRP3 inflammasome activation, and pyroptosis. Furthermore, MGO reduces the immunosuppressive activity of retinal pericytes and alters the VEGF/Ang2 ratio, contributing to endothelial dysfunction (Bento et al., 2010; Chandrakumar et al., 2023; Wang et al., 2024).

RAGE protein ligands

Finally, S100B and HMGB1 are two well characterized non-AGE, protein ligands for RAGE (Pachydaki et al., 2006; Juranek et al., 2022). S100B is expressed by astrocytes and serves as a biomarker of neuronal damage under oxidative stress. While decreased S100B levels have been noted in patients with peripheral neuropathy—suggesting a neuroprotective role, elevated S100B levels have been detected in serum and vitreous samples of patients with DR. Immunofluorescence studies have also shown elevated RAGE and S100B expression in diabetic retinas (Pachydaki et al., 2006). S100B–RAGE signaling induces VEGF production, which is a key factor in ocular neovascular diseases, including DR. Although primarily nuclear protein, HMGB1 is actively or passively secreted. Its levels are elevated in the vitreous fluid and epiretinal membranes of DR patients (El-Asrar et al., 2011; Abu El-Asrar et al., 2012). HMGB1 is implicated in optic nerve damage, angiogenesis, and inflammation in diabetes. Blocking HMGB1 signaling may offer protection against optic nerve damage. HMGB1 also upregulates signal transducer and activator of transcription-3 (STAT-3) in diabetic retinas (Mohammad et al., 2017), and its release from ARPE-19 cells under hypoxic conditions contributes to hypoxia-induced pathology in DR (Chang et al., 2017) (Fig. 3).

Lastly, advanced oxidation protein products (AOPP), which structurally and functionally resemble AGEs, also signal through RAGE. Formed during oxidative stress, AOPPs contribute to tissue damage, increase microvas-

RAGE (receptor for advanced end-products)
- Multi-ligand cell surface receptor and a member of immunoglobulin superfamily
- Expressed on many cell types, including neurons, epithelial cells, endothelial cells, and immune cells
- Physiologically at low levels in adult tissues, its expression is significantly upregulated at sites of inflammation

AGEs (advanced glycation end-products)
- Compound molecules formed by adding sugars to proteins or lipids during non-enzymatic glycation
- Might be exogenous (present in food) or endogenous (produced intracellulary, increasingly with biological aging)
- Primary ligands of RAGE; upon binding trigger RAGE conformational changes and intiate a series of downstream pathological pathways

HMGB1 (high mobility group box 1 protein)
- Multifunction protein – nuclear form acts as a transcription factor; when released from phagotic cells, acts as cytokine and increases inflammation
- Besides RAGE, binds to Toll-like receptors and participates in inflammatory pathways

S100B
- Calcium binding molecule, primarly expressed by glial cells
- Mainly a regulatory protein, involved in calcium homeostatis, cell survival and differentation
- When secreted at high concentration, binds to RAGE and triggers detrimental biochemical signaling axis, acting as danger/damage associated molecular pattern molecule

Diaph1
- Cytosolic protein mainly involved in regulation of actin and related cytoskeleton proteins
- Conditional ligand of RAGE, binds to its cytosolic tail and intitiate a cascade of molecular changes leading to cellular pathology and increased inflammatory response

Fig. 3. Short description of RAGE and its main ligands in physiology and pathology.

cular endothelial permeability, and promote fibrogenic responses. Elevated AOPP levels have been positively correlated with the severity of DR. Spectrophotometric analyses have demonstrated significantly higher AOPP levels in patients with DR (Baskol et al., 2008). In rats diagnosed with prediabetes, a significant increase in AOPP concentration was observed not only in serum but also in the retina, and melatonin supplementation reduced the concentration of these oxidized proteins (Djordjevic et al., 2018).

RAGE–Diaph1 Axis and Intracellular Signal Transduction

The interaction between RAGE and Diaph1 was first described by Prof. Schmidt and her team in 2008 (Hudson et al., 2008). In that study, authors described in detail the binding mechanisms between the cytoplasmic domain of RAGE and the formin homology 1 (FH1) domain of Diaph1 (Rai et al., 2012). The study proved to be crucial in elucidating RAGE signal transduction pathways and demonstrated that, for RAGE to effectively transduce extracellular signals into the cell, it must bind to Diaph1. Conversely, Diaph1 may execute its functions either in conjunction with RAGE or independently.

Since this discovery, substantial progress has been made in clarifying the role of RAGE-Diaph1 signaling in neuroinflammation and hyperglycemia (Ruiz et al., 2021; Theophall et al., 2025). A number of small-molecule RAGE-Diaph1 inhibitors have been patented (Manigrasso et al., 2021) enabling both experimental and clinical studies.

Recent studies have shown that Diaph1 is highly expressed in human gliomas (Zhang et al., 2017); however, detailed information regarding its cellular localization and Diaph1-mediated mechanisms of dysfunction in the rodent or human central nervous system (CNS) has not yet been fully elucidated. The RAGE-Diaph1 interaction has been studied extensively in the context of neurological complications of diabetes and Alzheimer's disease. It has been established that Diaph1 is essential for RAGE signal transduction, including activation of mitogen-activated protein kinases (MAPKs), Rho GTPases, and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathways (Hudson et al., 2008; Touré et al., 2012). The aberrant activation of these pathways carries substantial pathological implications. RAGE-Diaph1 interaction promotes the generation of ROS, induces cellular migration, upregulates inflammatory cytokines, and subsequently downregulates ATP-binding cassette (ABC) cholesterol transporters such as ABCA1 and ABCG1. These effects contribute to intracellular lipid accumulation and associated cellular dysfunction (Kumar et al., 2013; Daffu et al., 2015). Notably, as demonstrated by our research and that of our collaborators, the effects of RAGE-Diaph1 signaling are influenced by several factors, including but not limited to cell type, ligand form and concentration, and the duration of signal activation (acute *versus* chronic) (Derk et al., 2018) (Fig. 4).

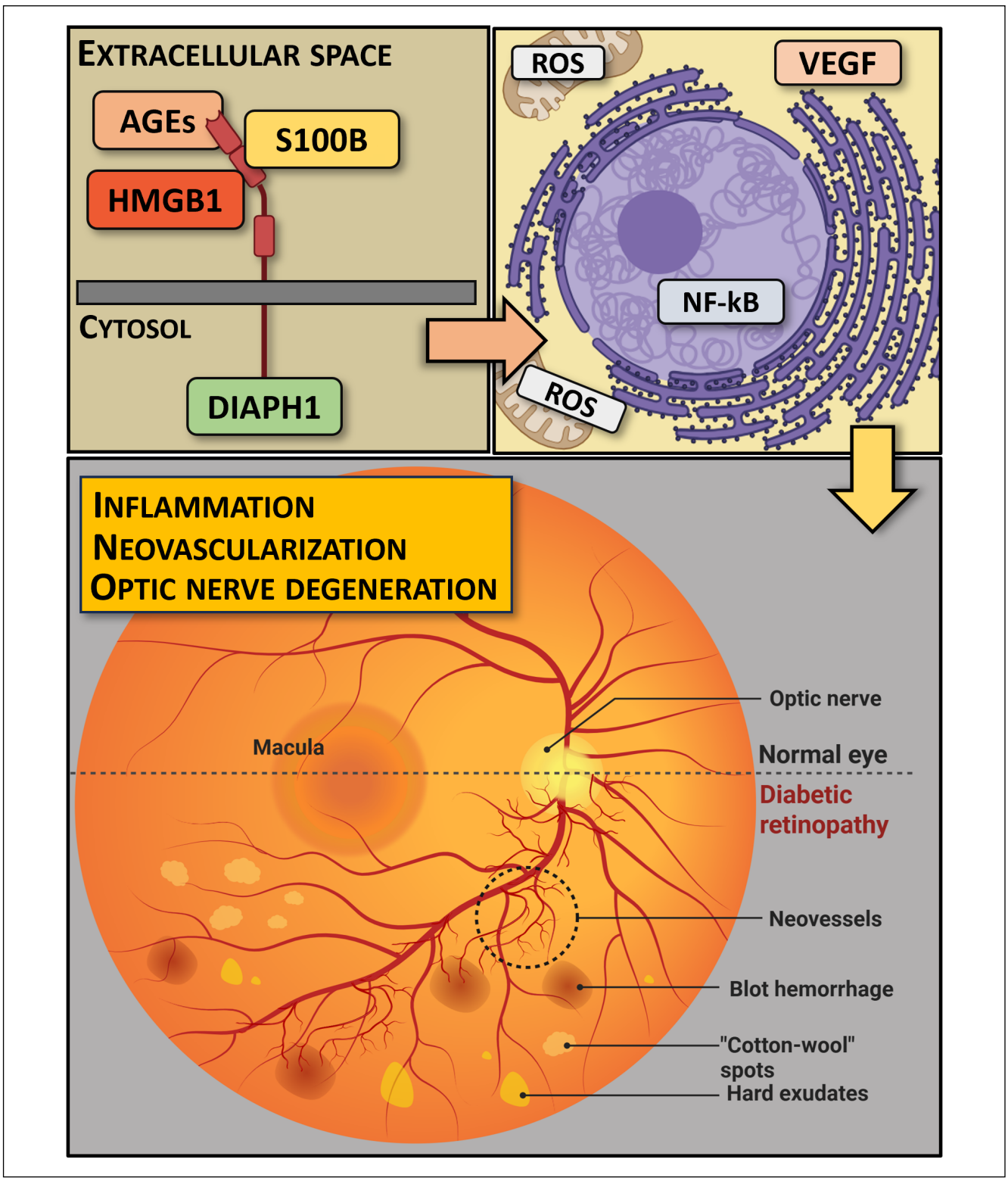

Fig. 4. RAGE-ligand pathways. Extracellular ligands such as AGEs, S100B, HMGB1 bind to RAGE's external domains, triggering its conformational changes, allowing it to bind to Diaph1, its cytosolic partner and initiating a series of intracellular events leading to the increased production of reactive oxygen species (ROS), activation of nuclear factor kappa B (NF-κB) and overexpression of vascular endothelial growth factor (VEGF) in hyperglycemia affected retina. Excessive presence of ROS and enhanced expression of NF-κB and VEGF triggers detrimental biochemical pathways, leading to retina inflammation and neovascularization and optic nerve degeneration, resulting in vision impairment and, if not, treated, vision loss. Created in BioRender. Juranek, J. (2025) https://BioRender.com/v79b6q9 (retina) and https://BioRender.com/akq9of5 (cell nucleus with mitochondria).

CONCLUSION

DR is a profound complication of diabetes that contributes to its morbidity. Currently, the most common form of management for DR is stabilization of glucose metabolism. Two promising new drugs, sulodexide and fenofibrate, have shown some efficacy in the management of DR. However, there remains a significant unmet need in the management of DR, which requires attention. Although therapies that target individual components of DR, such as vascular pathology, inflammation, and neurodegeneration, could be explored, a drug that modulates a common molecular axis impacting all these components is more likely to provide a comprehensive mechanism for managing DR. Current evidence, as described in this review, suggests that signaling through the RAGE/Diaph1 pathway may represent an axis implicated in all the pathological components of DR. We therefore suggest that small molecules targeted at this pathway are likely to be therapeutic candidates for DR.

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