REVIEW

Neuroinflammation and oxidative stress act in concert to promote neurodegeneration in the diabetic retina and optic nerve: galectin-3 participation

Henrique Rocha Mendonça[1,2,3,#], Raul Carpi-Santos[4,#], Karin da Costa Calaza[5,*], Ana Maria Blanco Martinez[1,*]

1 Laboratório de Neurodegeneração e Reparo, Departamento de Patologia, Programa de Pós-graduação em Anatomia Patológica, Faculdade de Medicina, Hospital Universitrio Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

2 Pólo Universitário Macaé, Unidade Integrada de Pesquisa em Produtos Bioativos e Biociências, Federal University of Rio de Janeiro, Macaé, Brazil

3 Laboratório Integrado de Morfologia, Instituto de Biodiversidade e Sustentabilidade, Núcleo de Pesquisas Ecológicas de Macaé, Federal University of Rio de Janeiro, Macaé, Brazil

4 Laboratório de Neurobiologia Celular, Instituto de Ciências Biomédicas, Centro de Ciências da Saúde, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

5 Laboratório de Neurobiologia da Retina, Departamento de Neurobiologia, Programa de Pós-Graduação em Neurociências, Fluminense Federal University, Niterói, Brazil

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Abstract

Diabetes is a lifelong disease characterized by glucose metabolic imbalance, in which low insulin levels or impaired insulin signaling lead to hyperglycemic state. Within 20 years of diabetes progression, 95% of patients will have diabetic retinopathy, the leading cause of visual defects in working-age people worldwide. Although diabetes is considered a microvascular disease, recent studies have shown that neurodegeneration precedes vascular changes within the diabetic visual system, albeit its mechanisms are still under investigation. Neuroinflammation and oxidative stress are intrinsically related phenomena, since macrophage/microglia and astrocytes are the main sources of reactive oxygen species during central nervous system chronic degenerative diseases, and both pathological processes are increased in the visual system during diabetes. The present review will focus on recent findings of the contribution of oxidative stress derived from neuroinflammation in the early neurodegenerative aspects of the diabetic visual system and their relationship with galectin-3.

Key Words: *diabetes; diabetic retinopathy; galectin-3; neurodegeneration; neuroinflammation; optic nerve; oxidative stress; retina*

Correspondence to:
Ana Maria Blanco Martinez, PhD, anamartinez@hucff.ufrj.br;
Karin da Costa Calaza, PhD, kcalaza@id.uff.br.

#These two authors contributed equally to this work.

orcid:
0000-0002-0821-5730 (Ana Maria Blanco Martinez)
0000-0003-1199-1826 (Karin da Costa Calaza)

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Introduction

Diabetes, a chronic and slow-progressive pathology, is one of the main world pandemics, estimated to affect 425 million people, or 8.8% of adults from 20–79 years, worldwide. Diabetes incidence keeps rising for decades, and the estimate for 2045 is that 629 million individuals aged 20–79 years will have diabetes. Besides that, about 212.4 million of these individuals have undiagnosed diabetes. Uncontrolled hyperglycemia in diabetes is one of the leading causes of cardiovascular disease, kidney failure, lower limb amputation and blindness. The global estimate of healthcare expenditure for 2017 was United States dollar 727 billion for individuals aged 20–79 years. The risk to develop most of the diabetes complication is higher with poorer hyperglycemia control. Therefore, the number of diabetes complications is possibly underestimated (International Diabetes Federation (IDF), 2015).

Diabetic eye disease results from a chronic hyperglycemic condition and comprises diabetic retinopathy (DR), diabetic macular edema, cataract, among others. DR is a leading cause of vision loss in working-age people (20–69 years) and about one in three diabetic patients has some degree of DR (International Diabetes Federation (IDF), 2015). The international association of the prevention of blindness estimates that 145 million individuals have some form of DR, worldwide (Kourgialis, 2017). DR affects more than 90% of patients within 20 years of disease progression and is the most common cause of acquired visual defects, being responsible for 1.9% of all cases of severe visual impairment and 2.6% of all cases of blindness.

Search Strategy

The search strategy employed to prepare this review was the retrieval of articles related to the themes of the sections of this Manuscript from the Medline database using different terms for each section. For Introduction, the term "Diabetes" was searched within the Title and Abstract fields. For

the Pathophysiology of Diabetes in the Retinofugal Pathway section, the term "Diabetes OR high glucose OR Hyperglycemia" were correlated (AND) to the search of the terms "retina OR optic nerve OR diabetic retinopathy" within the Title and Abstract fields. For the Inflammation, Oxidative Stress and Neurodegeneration in the Diabetic Retina section, the terms "Diabetes OR high glucose OR Hyperglycemia" were correlated to the search of the terms "retina OR optic nerve OR diabetic retinopathy" AND "inflammation OR neuroinflammation OR inflammatory OR oxidative stress OR reactive oxygen species OR reactive nytrosative stress OR reactive nitrogen species" within the Title and Abstract fields. For the Galectin-3 as A Mediator of Retina and Optic Nerve degeneration in Diabetes section, the terms "Diabetes OR high glucose OR Hyperglycemia" were correlated to the search of the terms "retina OR optic nerve" AND "Galectin-3" within the Title and Abstract fields. For the Treatment Strategies for Diabetic Visual Complications section, the terms "Diabetes OR high glucose OR Hyperglycemia" were correlated to the search of the terms "retina OR optic nerve OR diabetic retinopathy" AND "treatment OR drugs OR clinical trials". Qualitative analysis of the articles contents were performed to choose the ones that should be included in this Manuscript. Papers presenting data on humans, non-human primates and rodents were prioritized for the reviewing process, however *in-vitro* studies were also included to elucidate molecular and cellular mechanisms. Review articles and original articles published after 2014 were preferred, whereas articles published before 2010 were only included when they presented seminal data that were neither replicated nor reviewed in more recently published papers.

Pathophysiology of Diabetes in the Retinofugal Pathway

Retinal pathology

Classically, it is considered that vascular damage in the retina caused by hyperglycemia results in visual loss. The maintenance of a high concentration of glucose in the blood is able to induce an increase in basal membrane thickness. This leads to reduction of tight junction adherence between the endothelial cells, allowing the flow of molecules that in normal conditions would not pass through the blood-retinal barrier. Pericytes, which normally surround and support these cells, disappear. Later, capillary endothelial cells begin to multiply in the inner capillary wall, resulting in blockage of these blood vessels, forming microaneurysms, that disrupts in small hemorrhages. All these vascular alterations lead to ischemic events in the retina. The ischemic retina then releases pro-angiogenic factors that induce neovascularization. In most of the cases, these newly formed blood vessels are not functional and can worsen retinal damage, leading to the formation of micro-hemorrhages and retinal detachment, aggravating the patient's visual loss (Semeraro et al., 2015).

For a long period, a great deal of attention was given to the vascular alterations and the DR mechanisms behind these changes. Even the current treatments available target only vascular changes. However, there is now a great amount of evidence showing that the retina undergoes several changes even before the onset of clinically detectable DR.

During the early development of DR, several alterations in the neural retina are detected and observed, even prior to vascular ones (Barber et al., 1998). **Figure 1** identifies early changes during the first month of hyperglycemia, detected in the retina of streptozotocin (STZ)-induced diabetic rats, one of the most studied animal models. The hypothesis that hyperglycemia could damage the neural retina was proposed in the 1960s by Bloodworth (1962), who, based on the work of Wolter, proposed the following hypothesis: "Diabetic retinopathy is a complex degenerative disease of all the elements of the retina, probably caused by metabolic or enzymatic defects in cells, and are not related only to vascular supply" (Lieth et al., 2000). However, this hypothesis did not receive adequate attention and most studies on DR addressed the vascular aspect of the disease. Many studies have now demonstrated that hyperglycemia is able to induce changes in the neural retina (Barber et al., 1998, for review Lieth et al., 2000; Zafar et al., 2019). Electrophysiological studies in humans have shown that after two years of diabetes the sensitivity to contrast and color is affected. Changes in the retinal oscillatory potentials also occur in patients without detectable clinical (vascular) signs of DR (Coupland, 2004). In addition, multifocal electroretinography (Reis et al., 2014), color vision (Feitosa-Santana et al., 2010), pattern visual evoked potential (VEP) (Balta et al., 2017) and contrast sensitivity (Tiepei et al., 2015) showed alterations in patients that did not present retinal vascular changes. Together, these

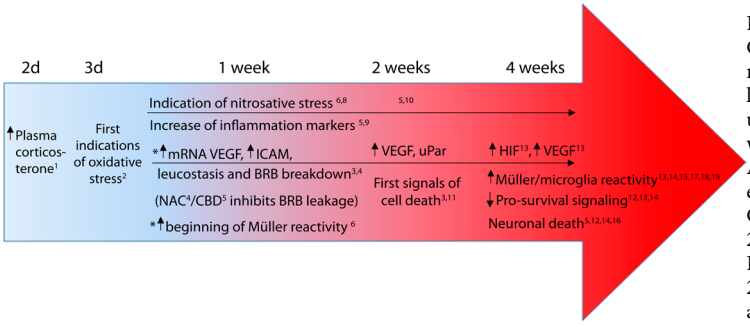

Figure 1 Summary of the major changes in the rat retina in the first 4 weeks of diabetes, induced by streptozotocin injection.
Since the temporal course of the modifications may be different depending on the animal model, we have decided to compare the early modifications using only this widely studied model. d: Days; ↑: increase; ↓: decrease; VEGF: vascular endothelial growth factor; ICAM: intercellular adhesion molecule 1; NAC: n-acetylcysteine; CBD: cannabidiol; BRB: blood retinal barrier; uPar: urokinase plasminogen activator receptor; HIF: Hypoxia-inducible factor. Thin long arrows indicate that the pointed changes prolong from 1 week up to 4 weeks. Numbers refer to references: 1. Magariños e McEween, 2000; 2. Obrosova et al., 2000; 3. Adamis e Bernan, 2008; 4. Abdouh et al., 2008; 5. El-Remessy et al., 2006; 6. Hernadez-Ramirez et al., 2017; 7. Roufail et al., 1998; 8. Do Carmo et al., 1998; 9. Carmo et al., 1999; 10. El-Remessy et al., 2003; 11. Gastinger et al., 2006; 12. Ali et al., 2008; 13. Fan et al., 2012; 14. Fort et al., 2011; 15. Lieth et al., 1998; 16. Barber et al., 1998; 17. Rungger-Brändle et al., 2000; 18. Krady et al., 2005; 19. Zeng et al., 2000; 20. Carpi-Santos and Calaza, 2018.

studies indicate that there are alterations in the functioning of the retina in early periods of diabetes, before the classic clinical vascular signs of DR are observed in the examination of the fundus of the eye.

Not only electrophysiological abnormalities are observed in the retina, but also morphological disturbances occur in neurons and glial cell types. These alterations precede vascular features of DR in humans, rats, dogs, among other species (Barber et al., 1998; Carrasco et al., 2007; Jiang et al., 2015). Increased apoptosis was detected in all retinal cell layers in samples of post-mortem diabetic patients who did not present vascular alterations (Carrasco et al., 2007). In experimental models, increase in terminal deoxynucleotidyl transferase dUTP nick end labeling-positive or caspase-3-positive cells, indicating apoptosis within the retina, occurred as soon as 2 weeks after diabetes induction in rats (Barber et al., 1998; El-Remessy et al., 2006; Gastinger et al., 2006; Roufail et al., 1998). Also in rats, there was an increase in Müller cell reactivity and in the number of microglia, and a decrease in amacrine cells and external photoreceptor segments (Szabó et al., 2017). Müller glial cells are important to blood-retinal barrier formation/maintenance and exhibit functions of maintaining the extracellular environment of retinal neurons. Studies evaluating retinas from diabetic post-mortem patients demonstrated increased glial reactivity (Carrasco et al., 2007). Interestingly, none of these diabetic patients presented vascular alterations, suggesting that the glial reactivity is a phenomenon that precedes the damage to the blood vessels of the retina. In rats, an increase in glial fibrillary acidic protein labeling, a marker of glial reactivity, was observed as soon as 7 days after diabetes induction (Hernández-Ramírez et al., 2017); an augment in glial fibrillary acidic protein-positive cell number after 1 month of diabetes was also detected (Rungger-Brändle et al., 2000). Although retinal blood vessels permeability in rats was detected in rats after 1 or 2 weeks of diabetes induction (Rungger-Brändle et al., 2000; El-Remessy et al., 2003; Abdouh et al., 2008), an increase in acellular capillaries was detected only after 2 months in human diabetes (Lin et al., 2017) and breakdown of the blood-retinal barrier has also been shown in juvenile diabetic patients without retinopathy. Interestingly, the depletion of Müller glia in the retina of mice produced blood-retinal barrier breakdown and vascular alterations, suggesting that glial dysfunction is a primary contributor to vascular disease (Shen et al., 2012).

Recently, it was also possible to show, by optical coherence tomography, that diabetic patients without any DR signs presented a reduction in retinal thickness, in the inner plexiform layer-ganglion cell layer and in the optical fiber layer, indicating neurodegeneration (Tiepei et al., 2015; Carpineto et al., 2016; Ng et al., 2016; Sohn et al., 2016; Pinilla et al., 2019), which confirm previous study using scanning laser polarimetry (Lopes de Faria et al., 2002). These data are in agreement with previous analysis of macular electroretinogram showing reduction in functional activities of postreceptoral neurons in diabetic patients, with no alteration of photoreceptor activity. Finally, several studies have shown that alterations in contrast sensitivity, oscillatory potential (Coupland, 2004), multifocal electroretinogram (Harrison et al., 2011; Santos et al., 2017), color vision (Andrade et al., 2014), pattern VEP (Heravian et al., 2012) preceded vascular retinopathy and worse with the progression of retinal vascular lesions. These data strengthen the hypothesis that neural changes precede vascular alterations at the beginning of DR pathology (**Tables 1** and **2**). Therefore, neural changes could be used for earlier diagnosis of the disease and could also be targets for treatment.

Optic nerve pathology

Besides the retinal complications, optic nerve pathology in diabetic patients has been known since 1920. Optic disc inflammation and edema were observed in patients with poor glycemic control, leading to delayed latency in the VEP. VEP waves represent conduction to subcortical nuclei and

Table 1 Alterations detected in diabetic patients without retinopathy

Parameters measured	References
Oscillatory potentials	Coupland (2004)
Contrast sensitivity	Tiepei et al. (2012), Reis et al. (2014)
Dark adaptation	Amemiya (1977)
Multifocal electroretinography	Harrison et al. (2011), Reis et al. (2014), Santos et al. (2017)
Color vision	Feitosa-Santana et al. (2010), Andrade et al. (2014), Reis et al. (2014)
Pattern visual evoked potential	Heravian et al. (2012), Balta et al. (2017)
Breakdown of the blood-retinal-barrier	Lin et al. (2017)
Optical coherence tomography	Tiepei et al. (2015), Carpineto et al. (2016), Ng et al. (2016), Sohn et al. (2016), Pinilla et al. (2019)
Scanning laser polarimetry	Lopes de Faria et al. (2002)

Functional approaches used to detect early alterations in retinas from diabetic patients without retinopathy.

Table 2 Molecular alterations detected in diabetic patients without retinopathy.

Molecular alterations	Altered parameters	References
Oxidative stress markers	↑Lipid peroxidation, nitrotyrosine, and ↓GSH, ↓GSH/GSSG ratio	Carrasco et al. (2007), Ali et al. (2008)
Cell death/survival signaling	↑Pro-apoptotic $p75^{NTR}$ receptor, ↑tyrosine nitration of the pro-survival TrkA receptor, ↓phosphorylation of TrkA and its downstream target (Akt); ↓ somatostatin levels	Carrasco et al. (2007), Ali et al. (2008)
Glial reactivity	↑GFAP staining	Carrasco et al. (2007)
Apoptosis	TUNEL staining	Barber et al. (1998), Carrasco et al. (2007)

Molecular markers altered in retinas from diabetic patients with no vascular changes. ↑: Increase; ↓: decrease; Akt: protein kinase B; GFAP: glial fibrillary acidic protein; GSH: gluthatione; GSSG: gluthatione oxidized; $p75^{NTR}$: p75 neurotrophin receptor; TrkA: tyrosine kinase receptor A; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling.

visual cortices. Since it was observed that VEP waves were normalized after glycemic control, the nerve conduction defects were clearly related to hyperglycemia. Besides, employing extensive electrophysiological evaluation, Parisi et al. (1997) have shown that optic nerve damage are not only present, but also precede retinal impairment. These authors have shown, by VEP analysis, that visual conduction delay in the optic nerve/tract was the first identified symptom, within the first year of disease. After 1 year, pattern-electroretinogram was also impaired, showing retinal ganglion cell (RGC) commitment. Finally, after 10 years of disease progression, oscillatory potentials and flash-electroretinogram were also impaired, indicating alterations in the inner nuclear layer and photoreceptors, respectively. Recently, Deák et al. (2015) corroborated these data, showing that 92% of type II diabetes mellitus patients presented VEP alterations, whereas only 60% of these patients presented pattern-electroretinogram abnormalities. Finally, studies have shown that childrens and adolescents with type 1 diabetes and adults with type 1 diabetes presented asymetric thickness of retinal fiber layer, suggesting that hyperglycemia results in degenerative events of the axons that will unite in the optic disc to form the optic nerve (Pekel et al., 2017a, b).

Animal studies were employed to unravel the mechanisms of the optic nerve pathology within diabetes. Scott et al. (1986) found decreased axon volume within the optic nerve of STZ-treated rats, 3 months after diabetes induction. The decrease in axon volume was associated with an increased density of blood vessels, arguing for a blood supply abnormality being responsible for the optic nerve pathology. Indeed, it was found that STZ-treated rats presented a reduced blood-flow and increased microvascular permeability after 3 months of diabetes (Zhao et al., 2010), that could lead to ischemic-hypoxic conditions, resulting in neurodegeneration, corroborating the delayed nerve conduction found in diabetic patients. Besides, Alemán et al. (2016) have found vascular thickness associated to elevated transcytosis and perivascular macrophages in STZ-induced diabetic rats. Additionally, the optic nerve head presents higher stiffness (Terai et al., 2011), probably impairing normal blood circulation within the optic central artery and vein.

Ino-Ue et al. (1998) found that Wistar rats' optic nerves presented axons of smaller diameter and thinner myelin sheaths, 3 months after STZ treatment. The reduced axon caliber might be related to the impaired axonal transport found in diabetic animals (Fernandez et al., 2012). The impairment of neurofilament transport in peripheral nerves of diabetic animals was shown to be dependent on the over-activity of the poIyol pathway. Indeed, inhibition of the polyol pathway through aldose reductase blockers spares axonal transport of RGC in rats, 3 months after STZ treatment. In addition, Kancherla et al. (2016) have shown reduced fractional anisotropy and increased radial diffusivity after 1 month of diabetes induction by STZ in rats, a period when chromium- and manganese-enhanced magnetic resonance imaging showed normal retinal organization and normal retinogeniculate axonal transport of manganese, suggesting that myelin impairment precedes axonal damage. Similarly, Aleman-Flores and Mompeo-Corredera (2018) showed decreased myelin thickness, increased myelin degeneration and increased number of internal mesaxons, suggesting increased myelin degeneration from 6 weeks after STZ-mediated diabetes induction in rats. In addition to the decrease in axon diameter and myelination abnormalities, axon number was also found to be reduced within the distal end of the optic nerve, 6 weeks after STZ treatment in mice (Fernandez et al., 2012). This reduced number of axons was correlated to increased astrocyte reactivity, reduced brain derived neurotrophic factor levels and disorganized myelination, and higher microglia/macrophage number within the optic nerve (Dorfman et al., 2015; Fernandez et al., 2012). Neuroinflammation causes proliferation of glial cells, glial scar formation and neuronal and glial cell death (Cerami et al., 2017); therefore, the investigation of its modulation are timely and of great interest.

Inflammation, Oxidative Stress and Neurodegeneration in the Diabetic Retina

Inflammation-induced damage in the diabetic retina

Within the central nervous system (CNS), the inflammatory response is delayed and is less intense than in the periphery. Its protective or toxic effect is dependent on the profile of secreted cytokines (Cui et al., 2009). Besides, the arousal and regulation of immune response in the brain are related to glial cells, such as microglia, astrocytes and Müller glia within the retina. Thus, depending on their activation profile, they can either amplify or reduce inflammation, therefore protecting or damaging the nervous tissue (Arnett et al., 2001).

Cell-mediated inflammatory response

Microglia is a highly inflammatory related cell type, with function analogous to macrophage, within the CNS (Rashid et al., 2018; Sorrentino et al., 2016). Microglia presents intermediate states ranging from anti-inflammatory and prohealing M2 polarization phenotypes to classic pro-inflammatory M1 profile (Lampron et al., 2013; Su et al., 2015). In physiological state, as well as in acute inflammation and retinal development, microglia monitor the neuronal microenvironment contributing to nervous tissue homeostasis (Arroba and Valverde, 2017) and can be neuroprotective (Prinz and Priller, 2014). However, under high glucose levels found within the retina, advanced glycation end products (AGEs) and reactive oxygen species (ROS) are found to activate microglia (Milne and Brownstein, 2013). The activation can be seen by its morphological differentiation, from a ramified to an amoeboid morphology (Young and Morrison, 2018). Studies in rodents have shown that microglia increases extracellular-signal-regulated kinase phosphorylation and nuclear factor-kappa B nuclear activation, culminating in increased levels of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-8 and IL-6. Besides, STZ-induced diabetic rats presented microglia/macrophage-dependent apoptosis of RGC, since it could be counteracted by the microglia/macrophage inhibitor minocycline. Macroglia, which also presents innate immune functions within the CNS, were also shown to be activated by high glucose. During diabetes, retinal astrocytes were activated, secreting IL-6, monocyte chemoattractant protein 1 and vascular endothelial growth factor (VEGF) (Shin et al.,

2014). Finally, Müller glia presented increased levels of AGE receptors in diabetic conditions, leading to the production of cytokines, such as TNF-alpha, IL-1beta, IL-6, monocyte chemoattractant protein 1, nitric oxide and VEGF (Yu et al., 2015). Therefore, glial cells communicate with each other and to neurons through secreted factors that indicate functional or pathological states, triggering coordinated responses (Jha et al., 2013; Vecino et al., 2016).

Cytokine-mediated inflammatory response

IL-1beta and TNF-alpha were shown to activate endothelial cells, which in turn increase intercellular adhesion molecule-1 membrane content. Intercellular adhesion molecule-1 binds to monocytes and neutrophils, via interaction with very late antigen 4 and CD18, favoring diapedesis and monocytes differentiation into macrophages. Additionally, IL-8 is a cytokine classically involved in neutrophil recruitment to inflammatory sites (Henkels et al., 2011), increasing its infiltration within the retina. Under hyperglycemic conditions found in the diabetic retina, neutrophils were shown to undergo NETosis, a distinct programmed cell death for neutrophils, that leaves extracellular traps with granules of myeloperoxidase to provide oxidative damage to eventual pathogens, but also damaging host tissue (Wang et al., 2018). Besides, monocyte chemoattractant protein 1 is a chemokine classically involved in monocytes recruitment to inflammatory sites, increasing its infiltration within the retina. Thus, monocytes might migrate from blood and differentiate into macrophages within the retina of diabetic rats, contributing to the disease pathological process. Microglia/macrophage were shown to be continuously activated from one to two months after diabetes induction, reaching a plateau by the third month (Chen et al., 2015). Retinal neuronal death was found to be stimulated by TNF-alfa-mediated caspase-3 activation (Costa et al., 2012), which might lead to visual deficits. Also, IL-6 induced STAT3 activation within retinal endothelial cells promotes VEGF production, leading to the vascular pathological aspects of DR (Jha et al., 2017). In addition, reducing inflammation of STZ-induced diabetic rats with glycyrrhizin (a glucocorticoid-like anti-inflammatory compound) also reverted nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2, reactive oxygen species and active caspase-3 positive apoptotic cells within the retina (Mohammad et al., 2015), revealing that hyperglycemia, neuroinflammation and oxidative stress-induced apoptosis are related processes in diabetes.

Therefore, during diabetes progression, the retina presents a highly inflammatory profile, showing an increase in the number of microglia/macrophage and a progressive shift from M2 to M1 profile, with high levels of pro-inflammatory cytokines, besides neutrophil infiltrate, Müller cell and astrocyte activation, leading to oxidative stress and neurodegeneration (Karlstetter et al., 2015; Cai et al., 2016).

Oxidative stress in the diabetic retina

The origins of hyperglycemia-induced damage can be related to neuroinflammation and oxidative stress (Barber et al., 2011). ROS production is a natural phenomenon of cellular metabolism. The maintenance of basal levels of cellular ROS is made by antioxidant systems, which are capable of neutralizing free radicals produced by the cells. These systems may be enzymatic (superoxide dismutase (SOD), glutathione peroxidase and catalase) or non-enzymatic (vitamin C, flavonoids and glutathione (GSH). The balance between ROS production and its neutralization by antioxidant systems is essential for the maintenance of cellular function, and an intense imbalance can generate excessive levels of these free radicals in the intracellular environment. This phenomenon is called oxidative stress. Oxidative stress can cause damage to DNA, proteins, carbohydrates and lipids due to reactions between free radicals of oxygen and these molecules. These cumulative damage caused by oxidative stress are associated with aging and several pathological processes (Kourgialis, 2017; Ma et al., 2017), including DR (Giacco and Brownlee, 2010).

Mitochondria are the main source of ROS in the cell and, in situations of hyperglycemia, ROS production is increased. One of the hypotheses that explain the initial increase of ROS in situations of hyperglycemia would be the increase of the activity of the citric acid cycle due to high glucose levels. In physiological situations, approximately 5% of the oxygen used in the oxidative phosphorylation chain is reduced to superoxide. However, in high glucose situations, due to the increased activity of the citric acid cycle, there is a greater availability of FADH2 and NADH to the mitochondrial electron chain. With the increased availability of these two electron donors, the limit of voltage gradient of the mitochondrial membrane is reached. Then, the transfer of electrons through the mitochondrial complex III is inhibited, causing the electrons to return to coenzyme Q, which transfers the electrons to the oxygen molecule, forming superoxide in an exacerbated magnitude, leading to oxidative stress. Mitochondria are organelles that have its own DNA (mitochondrial DNA), which encodes 13 proteins that are essential for the electron transport chain (Kowluru et al., 2015). This mitochondrial DNA, which has no histones, is located in close contact with the site of ROS generation, thus being susceptible to oxidative damages. In fact, recent studies in diabetes revealed that retinal mitochondria presented high levels of oxidized mitochondrial DNA, which is associated with compromised electron transport chain protein production (Mishra and Kowluru, 2014). Furthermore, mitochondria was shown to present structural damage in diabetes: it became swollen and there was a loss of membrane integrity, resulting in cytochrome C release into the cytosol, leading to cellular loss (Mishra and Kowluru, 2014; Tien et al., 2017). In addition to ROS produced in the mitochondria, there is also an increase in the production of cytosolic ROS in situations of hyperglycemia. In the cytosol, ROS formation is catalyzed primarily by the enzyme NADPH oxidase. This enzyme catalyzes the reduction of oxygen, which receives an electron, forming the superoxide radical, in a manner dependent on NADPH, and has its activity positively modulated by monomeric G proteins, Rac1 and Rac2 (Bokoch and Zhao, 2006). In the retina of diabetic rats, after a short period of hyperglycemia (15 days), there was an increase in Rac1 activity and NADPH oxidase 2 expressions concomitant with increased oxidative stress. It is important to note that

cytoplasmic ROS overproduction was detected prior to mitochondrial damage and dysfunction (Kowluru et al., 2014). Interestingly, when Rac1 activity was inhibited, increased oxidative stress induced by diabetes did not occur in the retina of these animals, demonstrating an important role of the NADPH oxidase 2 activation for the initial increase in ROS formation and cellular damage in retinas subjected to high glucose (Kowluru et al., 2014). In agreement, Masser and coworkers have shown that retinal deficits already occured in rats after 3 months of diabetes without marked mitochondrial dysfunction (Masser et al., 2017).

Increase in oxidative stress is also related to biochemical pathway alterations. Studies have shown that after overproduction of ROS, damage to cellular DNA occurs. In response to such damage, several DNA repair enzymes are activated, such as poly (adenosine diphosphate (ADP)-ribose) polymerase. Poly (ADP-ribose) polymerase produces nicotinic acid and ADP ribose. ADP ribose, in the nucleus, is capable of interacting with the enzyme glycerol-3-phosphate dehydrogenase. Once bound to ADP ribose, glycerol-3-phosphate dehydrogenase is inhibited. This enzyme is responsible for the glycolytic pathway step in which glyceraldehyde-3-phosphate is converted to 1,3-bisphosphoglycerate. Therefore, glycerol-3-phosphate dehydrogenase inhibition leads to an accumulation of glycolytic intermediates in the cytoplasm. With this accumulation, glycolytic intermediates are used in other biochemical pathways such as polyol pathway, advanced glycation species formation (AGEs), increased protein kinase C activation and hexosamine pathway (Giacco and Brownlee, 2010). These metabolic pathways aggravate ROS production, leading to a positive feedback in oxidative stress. Mechanistically, it was shown that oxidative stress promotes calcium entry and RGC neurodegenration independent from DNA fragmentation and caspase-3 activation, in a process known as oxytosis.

Besides increase in ROS production, the intracellular antioxidant capacity is also compromised in DR progression. In physiological situations, ROS are neutralized by endogenous antioxidants molecules, such as GSH and enzymes, for example SOD. However, it has been shown a decrease in SOD, as well as GSH peroxidase, reductase and transferase activities as soon as three days after diabetes induction (Obrosova et al., 2000). SOD levels were also reduced in the retinas of mice, 4 months after diabetes induction (Zhong and Kowluru, 2011) and the activity of this enzyme was also impaired. Moreover, Mn-SOD (a manganese dependent SOD isoform) overexpression in mice had a protective effect, and these animals did not develop the diabetes induced histopathologic signs. Accordingly, a polymorphism in Mn-SOD gene, which decreases its activity, was associated with a worse prognostic in the development of DR in humans. Also, during the initial stages of hyperglycemia (3–6 weeks), GSH levels were found to be reduced in the retina of diabetic rats (Carpi-Santos et al., 2016; Carpi-Santos and Calaza, 2018) and remained impaired in later stages of diabetes (6–8 months) (Carpi-Santos and Calaza, 2018). This phenomenon could be a result of DR impact in the pathway of GSH production. The system responsible for cystine uptake, which is converted to cysteine in the cell (a limiting substrate for GSH production) and the enzyme for GSH synthesis (glutamine cysteine ligase) were found to be impaired in the retina of diabetic rats (Carpi-Santos and Calaza, 2018; Zhong et al., 2013). Thus, oxidative stress is a major feature of DR development. However, as discussed above, there are multiple factors associated with ROS increase, such as augment in mitochondrial and cytoplasmatic ROS production, cellular biochemical alterations and reduction in antioxidant capacity (**Figure 2**). To make a difficult problem worse, besides oxidative stress, an increase of nitric oxide is also described in the development of DR (Carpi-Santos et al., 2017; Do Carmo et al., 1998; El-Remessy et al., 2003; Opatrilova et al., 2018) which can lead to nitrative/nitrosative stress. In addition, as it will be discussed in the next topic, DR is also considered an inflammatory disease. This multifactorial feature creates a big challenge for the development of an efficient treatment for this disease.

As oxidative stress is a major factor in the complications that result from diabetes, many groups have been studying the influence of diabetes on Nrf2, a transcptional factor activated by oxidative stress, in several tissues (Dieter, 2014). Nrf2 binds to the antioxidant responsive element DNA region and induces the upregulation of several genes associated with antioxidant response, such as the enzymes for GSH synthesis. In the context of DR, Nrf2 activity has been shown to be increased after 3 months of diabetes (Song et al., 2016); however, Zhong et al. (2013) have shown that after longer periods of diabetes (6 months), Nrf2 activity in rat retina was impaired. Carpi-Santos and Calaza (2018) have shown that the binding of Nrf2 to the antioxidant responsive element region oscillates during DR development: at 1 month was reduced; after 2 months, Nrf2 binding was similar in diabetic and normal rats; however, after 6 months of diabetes, the levels of Nrf2 bound to the antioxidant response element DNA region were again decreased in the retina of diabetic animals. In addition, the ablation of Nrf2 by knockout in mice has been shown to aggravate the progression of this disease. These animals presented lower levels of protective enzymes against ROS and exhibited worse performance in visual acuity tests (Xu et al., 2014). With that in mind, some groups are investigating the effect of Nrf2 modulation during DR. Deliyanti et al. (2018) demonstrated that a Nrf2 activator (dh404) treatment increased the antioxidant capacity in diabetic rat retina, prevented vascular leakage, inhibited the upregulation of vascular permeability inductors and reduced the levels of the pro-inflammatory cytokines, IL-6 and TNF-alpha (Deliyanti et al., 2018). Furthermore, diabetic rats that received sulforaphane, a Nrf2 activator, presented higher levels of antioxidants enzymes and reduced levels of pro-inflammatory cytokines in the retina when compared to rats that did not receive sulforaphane (Li et al., 2018). Concerning neuroinflammation, it have been shown that the phytochemicals thymoquinone and kolaviron exert Nrf2-dependent anti-inflammatory effects in microglial cells, decreasing TNF-alpha, IL-6, nitric oxide and prostaglandin E2 release after lipopolysaccharides stimulus (Onasanwo et al., 2016; Velagapudi et al., 2017). These studies indicate that Nrf2 activation could be a possible candidate for DR treatment in the future.

Considering that both oxidative stress and neuroinflammation trigger neurodegeneration, which precedes the vascular pathology of DR, it is unlikely that treatment of the vascular changes only can recover the necessary conditions for the survival and normal functioning of the visual system. Therefore, novel pharmacological targets that participate within the aforementioned processes are required to achieve improvements in DR management.

Galectin-3 as a Mediator of Retina and Optic Nerve Degeneration in Diabetes

Galectins are multivalent lectins of approximately 130 aminoacids that present a single polipeptide chain, containing one or two carbohydrate recognition domains, being able to bind beta-galactosides. In mammals, 15 types of galectins were identified and grouped into prototypes - galectins 1, 2, 5, 7, 10, 11, 13, 14 and 15-, tandem - galectins 4, 6, 8, 9 and 12- and chimera - galectin-3 (Barondes et al., 1994). Galectin-3 is synthesized in cytoplasmic free ribosomes and can be targeted to different cellular compartments or also to the extracellular space via endoplasmic reticulum and Golgi apparatus (Rabinovich et al., 2012). It regulates several biological processes, such as cell adhesion, proliferation, apoptosis, tumor progression, oxidative stress, inflammation and innate and adaptative immune system modulation. Its different cell type expression, sub-cellular compartimentalization and different post-translational modification may account for its opposite actions during different physiopathological processes, such as stimulation *versus* inhibition of apoptosis, or its pro- *versus* anti-inflammatory action (Jeon et al., 2010). Indeed, even in the nervous system galectin-3 exerts opposite actions after traumatic lesions, stimulating inflammation, degeneration and regeneration of the peripheral nervous system, while reducing inflammation and degeneration within the CNS (Abreu et al., 2016; Mostacada et al., 2015).

Galectin-3 has been increasingly related to the pathogenesis of diabetes, and has been identified as a novel serum marker of pre-diabetes and a diabetes risk factor in humans (Yilmaz et al., 2015). Its content was shown to be chronically increased in pancreatic and peripheral blood macrophages after diabetes development in db/db transgenic mice (Cucak et al., 2013). Mechanistically, galectin-3 directly binds to mouse insulin receptor, antagonizing its downstream metabolic signaling pathways, leading to insulin resistance and glucose intolerance (Li et al., 2016). In a recent study, galectin-3 was identified as a pivotal target on diabetes-induced neurodegeneration within the mice visual system (Mendonça et al., 2018). Indeed, galectin-3 was found to be expressed in Müller cells in the normal retina and in microglia/macrophage after lipopolysaccharides-induced neuroinflammation in rodents (Bauer et al., 2016). Besides, it has been shown that AGE-treated mice present a galectin-3 dependent reduction of retinal neovascularization on a proliferative retinopathy animal model, suggesting that it also plays a role in the vascular phase of DR. However, Wesley and coworkers have shown that galectin-3 induces microglia angiogenic potential after an ischemic human umbilical endothelial vein culture model (Wesley et al., 2013). Indeed, galectin-3 knockout mice prevented later vascular retinal damage that was found in wild-type (WT) mice after diabetes induction. Within the neural retina, it was shown that RGC survival, due to decreased apoptosis, and optic nerve fibers preservation, due to less microglia/macrophage within the lesion site, were enhanced in galectin-3 knockout mice, after optic nerve crush (Abreu et al., 2017). Additionally, after spinal cord compression, galectin-3 knockout mice presented better white matter preservation with less infiltration of neutrophils, and less microglia/macrophage content. These microglia/macrophages were mainly shifted to an

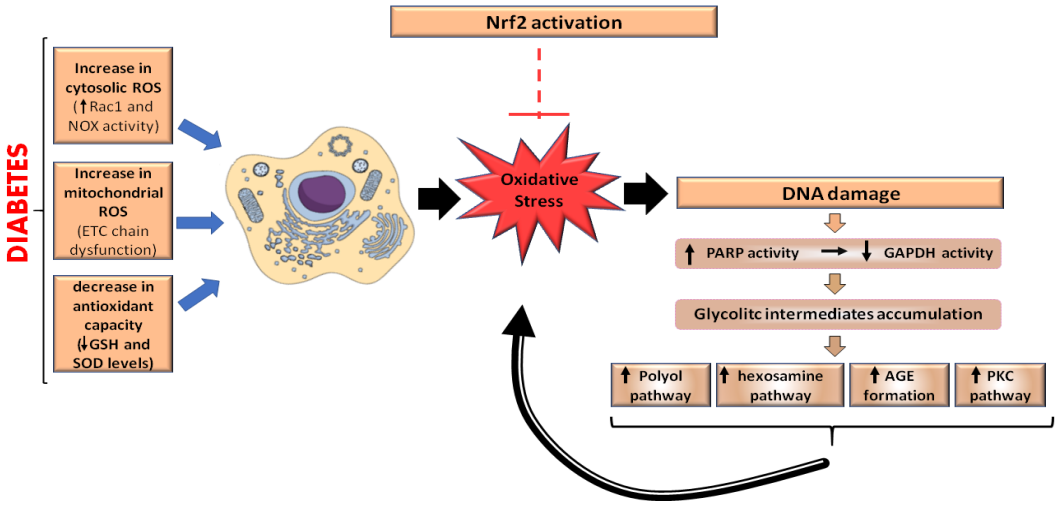

Figure 2 Multiple pathways for oxidative stress in diabetes.
During diabetes, there is an increase in reactive oxygen species (ROS) production due to cytosolic increased nicotinamide adenine dinucleotide phosphate oxidase activity, dysfunctional mitochondrial electron transport chain and a reduction of cellular antioxidant capacity, such as glutathione (GSH) and superoxide dismutase (SOD), leading to oxidative stress. Oxidative stress leads to DNA damage, which activates DNA repair enzymes, such as poly (adenosine diphosphate-ribose) polymerase (PARP). This results in ADP increase and glycerol-3-phosphate dehydrogenase (GAPDH) inhibition. The impairment of GAPDH results in glycolytic intermediates accumulation. Consequently, these molecules are used in other biochemical pathways, such pollyol and hexosamine pathways, advanced glycation end product (AGE) formation and also increase protein kinase C (PKC) activation. All these pathways are associated with an increase in oxidative stress, leading to a positive-feedback of ROS production. Nrf2 is a transcriptional factor that is associated to an antioxidative response. In that way, activation of Nrf2 pathway could be a possible mechanism to break the vicious cycle of ROS production in diabetic retinopathy development. ETC: Electron transport chain.

anti-inflammatory profile, due to arginase-1 higher staining than in WT lesioned mice, leading to reduced nitric oxide production. These features led to better motor behavior, two months after lesion (Mostacada et al., 2015). Alternatively, mouse hyperglycemia increased nitric oxide levels, leading to S-nytrosilation of insulin degrading enzyme, which may dysregulate insulin signaling. Besides, insulin degrading enzyme also degrades beta-amyloid peptide, that thus accumulates, leading to synapse potentiation impairment and loss (Akhtar et al., 2016). It was recently shown that secreted galectin-3 binds to toll-like receptor 4, increasing the secretion of IL-1beta, IL-6, TNF-alpha and nitric oxide, contributing to neurodegeneration after traumatic brain injury in mice (Yip et al., 2017). Moreover, since it was shown that galectin-3 is involved in the internalization of AGEs into cells, its blockade may also reduce oxidative stress-mediated damage. Indeed, galectin-3 was shown to stimulate NADPH oxidase 2 burst in human neutrophils that had undergone migration out of the bloodstream (Karlsson et al., 1998) and to promote myeloperoxidase secretion on a neutrophil chemoattraction assay (Forsman et al., 2008). Thus, galectin-3 stimulates the production of nitric oxide from inflammatory cells, leading to tyrosine nitration, and enhances neutrophil production of the highly reactive superoxide anion and hypochlorous acid from NADPH oxidase 2 and myeloperoxidase activity, respectively. Therefore, galectin-3 seems to be a pivotal molecule triggering both pathological processes, and its modulation might be a useful tool to prevent diabetic visual complications.

Since galectin-3 has emerged as a pivotal neuroinflammatory modulator, the study of its role in diabetic optic neuropathy has been elucidative. It was recently described that galectin-3 knockout mice prevented RGC death that normally occurs two months after STZ-mediated diabetes induction in mice, via apoptosis reduction in the ganglion cell layer. Besides, myelin staining within the optic nerves revealed a more rectilinear pattern in galectin-3 knockout mice than in WT mice after diabetes, suggesting a better-preservation of nerve fibers. Indeed, ultrastructural analysis revealed more myelinated nerve fibers within the distal end of the optic nerve when compared to WT animals, after diabetes induction, revealing that both axon and cell bodies were preserved, which can reflect in better visual system functioning. Concomitantly, it was observed that both reactive astrocytes and macrophages were reduced within the distal portion of the optic nerves of galectin-3 knockout mice, but microglia content was the same between groups, suggesting that macrophage chemotaxis, infiltration and/or proliferation were impaired in galectin-3 knockout diabetic mice. These microglia/macrophages presented ramified morphological profile, suggestive of surveillance state, whereas WT diabetic animals presented intense amoeboid morphology, suggestive of activation. The microglia of galectin-3 null mice were less pro-inflammatory than WT mice derived microglia, since it was found less inducible nitric oxide synthase activation within galectin-3 knockout optic nerves. Therefore, these findings point to a pro-inflammatory role of galectin-3 during diabetes within the visual pathway, that leads to retinofugal nerve fibers and cell bodies degeneration (Mendonça et al., 2018). Similar findings were obtained by Manoucherian and collaborators in a murine model of hypoperfusion-induced retinal degeneration (Manoucherian et al., 2015). A summary of the actions of galectin-3 in the mediation of neuroinflammation and oxidative stress is presented in **Figure 3**. Thus, galectin-3 emerges as a potential target to diabetic control of optic nerve pathology.

Treatment Strategies for Diabetic Visual Complications

Currently, there are only treatments directed to vascular features of DR, and no treatment directed to the optic nerve pathology or non-vascular retinal symptoms, despite the findings that they precede DR. The best way to prevent diabetic ocular complications development is through rigid glycemic control. However, controlling glycemic levels is an arduous day-to-day task and diabetic patients end up experiencing periods of hyperglycemia. In fact, little is done regarding the visual treatment of these patients until DR is already in advanced stages. Therefore, the available treatments aim to prevent neovascularization in the retina, which is harmful to the tissue. The most common treatment is laser photocoagulation, used for cauterizing the hemorrhagic blood vessels and ischemic regions of the retina, inhibiting the release of angiogenic factors. With this technique, the progression of visual loss is decreased, but there is no visual recovery. In addition, there are some side effects, such as loss of peripheral vision, decreased visual acuity and increased formation of macular edema (Simó and Hernández, 2015), possibly due to the observed thinner peripapillary nerve fiber layer and optic nerve neuropathy, suggestive of RGC soma and axons degeneration. Another therapy used is intravitreal injection of steroids, due to its anti-inflammatory and anti-angiogenic action, as well as anti-VEGF. As VEGF induces angiogenesis and increases vascular permeability, favoring the breakdown of the blood-retinal barrier and the formation of edema, its inhibition has been beneficial in the treatment of patients with proliferative DR. One problem with these therapies is that, since these agents have a short half-life, multiple injections are necessary so that the concentration of these molecules remains at therapeutic levels. This large number of injections can cause harmful consequences, such as inflammatory events, retinal detachment and intravitreal hemorrhages (Bandello et al., 2013; Espírito-Santo et al., 2012). In addition, anti-VEGF injections only target vascular problems, leaving neural disturbances without treatment.

The treatments described above are important to avoid the progression of DR, however, new approaches are necessary for a better outcome. Since neurodegenerative, oxidative and inflammatory processes precede vascular modifications in DR, drugs that inhibit these pathways have been tested. Examples are aminoguanidine, an inhibitor of advanced glycation species pathway, aspirin, an inhibitor of inflammatory pathways and the systemic administration of various antioxidants. However, the results of these clinical studies were either inconclusive or discontinued due to side effects. Therefore, further studies on the early pathological processes of the DR, such as neuroinflammation-related oxidative stress, are needed so that new effective therapeutic approaches are

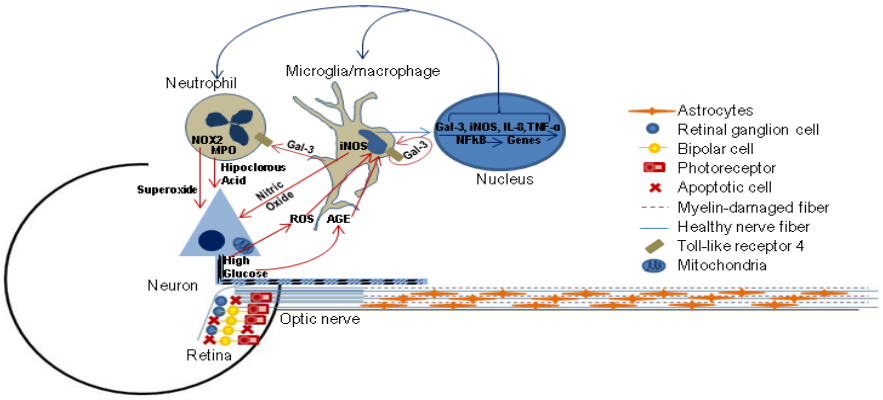

Figure 3 Proposed mechanisms by which neuroinflammation and galectin-3 (gal-3) mediates neurodegeneration in the diabetic visual system.
Hyperglicemic state increase advanced glycation end product (AGE) and reactive oxygen species (ROS) production, activating microglia/macrophage expression of gal-3 and other pro-inflammatory cytokines through nuclear factor-kappa B (NFkB) activation. Gal-3 binds to Toll-like receptor 4, induces macrophage and neutrophil recruitment, nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and myeloperoxidase (MPO) activity, producing the ROS superoxide and hipoclorous acid. Tyrosine nitration, oxidative stress and pro-inflammatory cytokines lead to axons collapse through impaired axonal neurofilament transport and neuron apoptosis in all retinal layers. Astrocytes proliferate and axons and myelin sheaths undergoes degeneration along the optic nerve. IL: Interleukin; iNOS: inducible nitric oxide synthase; TNF: tumor necrosis factor.

created. Since galectin-3 inhibition is currently being tested in clinical trials to treat non-alcoholic steatohepatitis, solid tumors, plaque psoriasis and atopic dermatitis (Chou et al., 2018; Musso et al., 2017), its application in clinical trials against the neurodegenerative aspects of diabetes are encouraged by the preclinical studies presented in this review.

Conclusions

Diabetes cause retinal pathological neurodegeneration, followed by vascular proliferative pathology. Both phases of the disease seem to be mediated by inflammation and consequent oxidative stress. Therefore, this review shed light to the relationship of two pathological processes that might act in concert inretinal pathology progress in diabetic patients, and the investigation of how their mechanisms, particularly the role of galectin-3, might foment the identification of novel targets for interventions that can eventually stop DR progression.

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