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Review

NF-κB Involvement in Glaucoma-Associated Neuroinflammation: Focus on Glial Cells

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Abstract

Glaucoma is a complex neurodegenerative disease characterized by the progressive loss of retinal ganglion cells (RGCs) and optic nerve damage. Both mechanical and vascular factors are believed to contribute to the etiology of glaucoma. However, the underlying pathogenic mechanisms are not yet fully understood. In this article, although it is a single component of a multifactorial condition, we argue that neuroinflammation is a significant factor in glaucoma pathogenesis. Glaucoma, at present, is recognized as a neurodegenerative disorder sharing common neuroinflammatory mechanisms with classical neurodegenerative diseases. The involvement of classical immune signaling pathways, such as TLRs and NF-κB, as well as proinflammatory cytokines like TNF-α, aligns glaucoma with other neurodegenerative diseases where inflammation is pivotal (e.g., Parkinson's and Alzheimer's diseases). As such, glaucoma should be considered not only an ocular pressure disorder but also a neurodegenerative condition with a strong immune component. This perspective opens new avenues for novel therapeutic intervention, including the targeting of glial cells or modulators of inflammatory signaling. However, the complexity of microglial phenotypes and the timing of their activation relative to astrocytes remain areas that require further clarification. The current M1/M2 paradigm is acknowledged as overly simplistic, highlighting the need for more refined and nuanced models. Although oxidative stress and other interconnected signaling, such as STAT3, are involved in the pathogenesis of glaucoma, here, we focus on the role of the NF-κB signaling pathway within the glaucomatous condition with a special focus on the main characters fostering the neuroinflammation.

Keywords: glaucoma; neuroinflammation; microglia; NF-κB; Müller cells; astroglia

1. Glaucomatous Disease and Neuroinflammation

Glaucoma is a chronic neurodegenerative disease characterized by the progressive degeneration of retinal ganglion cells (RGCs), loss of synapses, optic nerve damage and corresponding visual field defects [1]. Elevated intraocular pressure (IOP) is a well-known risk factor; however, glaucomatous neurodegeneration also occurs in patients with normal IOP, a condition commonly referred to as normal tension glaucoma (NTG). The evidence that NTG patients can still develop glaucoma points to mechanisms beyond mechanical pressure, with neuroinflammatory pathways emerging as central contributors (Fig. 1).

Genetic factors have been identified as prodromal in the development of glaucomatous dysfunction (e.g., MYOC, OPTN, CYP1B1). Furthermore, it has been demonstrated that key genes contribute to the onset of the neuroinflammatory state associated with the disease. Gain-of-function mutations in the pro-inflammatory gene *TBK1* play a crucial role in driving neuroinflammation in glaucoma pathogenesis, independent of IOP elevation [2–4]. Moreover, genome-wide association studies (GWAS) have implicated the ATP-binding cassette (ABC), subfamily A member 1 (ABCA1) gene in primary open-angle glaucoma (POAG), the most commonly diagnosed form of glaucomatous dysfunction [5,6]. ABCA1 is expressed in glaucoma-relevant ocular tissues such as the iris, ciliary body, retina, optic nerve head, optic nerve and trabecular meshwork. It has been demonstrated that ABCA1 may regulate neuroinflammation and neurodegeneration in several murine models, and some studies have shown its involvement in retinal pathogenesis and POAG [7,8]. ABCA1 has been implicated in retinal inflammation and RGC apoptosis, and has also been shown to play a role in IOP regulation through modulation of aqueous humor dynamics [9,10].

The inflammatory process involves the activation of resident glial cells, the production of proinflammatory cytokines and chemokines, and the infiltration of peripheral cells into the central nervous system due to the disruption of the blood–brain barrier. Initially, this response serves as a

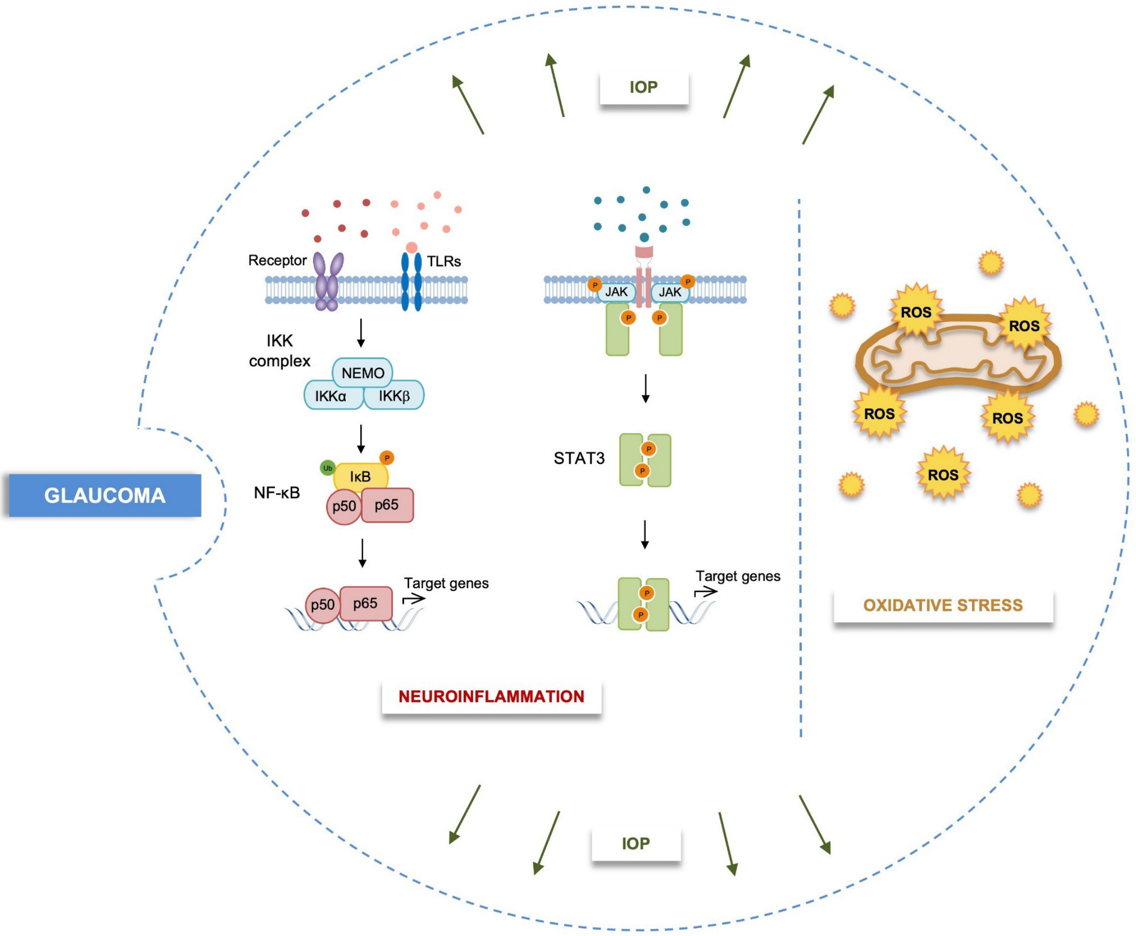

Fig. 1. Schematic representation of multifactorial pathogenic processes involved in glaucoma. Neuroinflammation, oxidative stress and biomechanical dysfunction are key factors in the disease onset and progression. IOP, intraocular pressure; IKK, IκB kinase complex; ROS, reactive oxygen species.

protective mechanism against various pathogens [11]. Glial cells continuously monitor the retina microenvironment and immediately respond to even minor changes to maintain tissue homeostasis. Macroglia (astrocytes and Müller cells) and microglia are resident immune cells that perform innate immune functions within the retina and optic nerve [12]. In the healthy, undamaged retina, these cells provide nutritional and structural support, participate in metabolism and regulate homeostasis. They also coordinate with each other to regulate neuronal activity through phagocytosis and the secretion of inflammatory cytokines and neurotrophic factors [13]. Functional dysfunction and neuronal damage occur when this homeostasis is perturbed and glial cells are unable to return to their resting state, as demonstrated by morphological, functional and molecular deregulations. This process is commonly referred to as “reactive gliosis” and is marked by specific morphological features such as hypertrophic cell bodies and thickened processes [14–16]. The dynamic interplay between microglia and macroglia further complicates the inflammatory milieu, potentially creating feedback loops that can either exacerbate or resolve damage [17]. Overall, these findings strongly suggest that glial cells are a driving force in the retina’s inflammatory process, and a deeper understanding of their role within the glaucomatous dysfunction could potentially support the identification of new therapeutic approaches.

2. Macroglia and Microglia: The Main Characters

Recent findings indicate that glaucomatous optic neuropathy is a neurodegenerative disorder that shares neuroinflammatory mechanisms with classical neurodegenerative diseases, highlighting the role of glial cell-mediated neuroinflammation in the pathophysiology of glaucoma [18,19].

Glial activation is crucial for restoring tissue homeostasis, facilitating repair and providing neuroprotection in the central nervous system (CNS), where astrocytes and microglia mediate the innate immune response [20]. The strong interplay between neurons and glial cells suggests that a dysfunction in either can result in harmful processes that may disrupt neuron–glia communication or jeopardize neuronal health [21,22]. The retina is an immune-privileged site where the impact of the systemic immune system is strictly regulated [23]. This immune privilege helps maintain retinal homeostasis and protects it from persistent and detrimental inflammation.

At least three types of glial cells exist in the mammalian retina: Müller cells and astrocytes, collectively referred to as macroglia, and microglia. Each of these cell types plays distinct roles in supporting retinal function and responding to injury or disease by carefully modulating immune responses. Astrocytes and microglia are now recognized to display various activation phenotypes, with their shift from protective to potentially harmful roles closely associated with the severity and progression of neurodegeneration [24].

Microglia are the resident immune cells of the CNS, including the retina, where they are found in several layers such as the nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL) and outer plexiform layer (OPL), acting as neuropathological sensors and as a first line of defense against injury. Microglia originate from primitive erythromyeloid progenitors that enter the CNS via the primitive bloodstream during early embryonic development.

Microglial cells can defend neural tissue from harmful stimuli like pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by detecting them through their specialized receptors, including TLRs [25,26]. In response to neural damage, microglia undergo morphological changes, proliferate, migrate and release inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-18, IL-23, TNF-α, CCL2, CXCL10, reactive oxygen species (ROS) and matrix metalloproteinases (MMP9 and MMP3), which can exacerbate neuronal loss and dysfunction [27,28].

In the context of glaucoma, reactive microglial cells initially engage in the phagocytosis of debris from damaged RGCs, thereby contributing to maintaining a toxin-free microenvironment. Additionally, these cells release neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF), which provide neuroprotection and promote tissue regeneration [29].

A rapid increase in IOP is able to induce changes in microglial morphology, such as retraction of processes, enlargement of the soma and increased expression of activation markers like CD68, in just 60 minutes [30]. Activated microglia produce pro-inflammatory and cytotoxic molecules, including complement factors, nitric oxide (NO), TNF-α, IL-6 and increased MHC I and II expression, all of which contribute to neurotoxicity and propagation of neuroinflammation in glaucoma. TNF-α is reported to increase in glaucoma patients and is associated with microglial activation and neuronal damage [31]. Gregory *et al*. [32] observed that in glaucomatous DBA/2J mice, high levels of TNF-α and an increased expression of the membrane-bound form of Fas ligand (mFasL) on microglia trigger apoptosis of RGCs via their Fas receptor. Pharmacological inhibition or genetic deletion of TNF-α or Fas ligand reduces microglial activation and protects RGCs [32,33].

Indeed, microglial activation is one of the earliest events in glaucoma, preceding RGC loss, as demonstrated in the DBA/2J animal model, where early microglial alterations correlate with the extent of neurodegeneration. Treatments that inhibit microglial activation, like minocycline, have been shown to reduce RGC death in this model, underscoring the critical role of activated microglia in the pathogenesis of glaucoma [16,34,35]. Overall, these findings highlight the role of microglial activation in glaucomatous neurodegeneration. Within this context, it is now widely accepted that this microglial-activation status in the CNS can shift among a plethora of phenotypes (M0-M1-M2a-M2b-M2c-M2d) that may exacerbate the neurodegeneration or rescue the stress-induced damage with a strong neuroprotective effect. These microglia subsets are conventionally divided into M0 (resting), M1-like (classical activated or pro-inflammatory) induced by lipopolysaccharide (LPS), interferon-gamma (IFNγ) and TNF-α, and M2-like (alternative activated or anti-inflammatory) induced by IL-4, IL-10 and IL-13 [36,37]. Other classifications take into account the morphology and activation states of microglia [38,39] and a transcriptomics-based approach [40,41], thus showing a more complex but more specific description of the different phenotypes.

Retinal astrocytes mainly reside in the NFL and GCL layers and are classically identified by the expression of Glial fibrillary acidic protein (GFAP), vimentin and nestin. Paired box 2 (Pax2) and SRY-Box Transcription Factor 2 (Sox2) instead are used as nuclear markers of astrocytes, which are present as well in the optic nerve [13,42–48].

In order to counteract glaucomatous dysfunction, the morphological structure of astrocytes, characterized by long processes that envelop RGCs, plays a structural role in counteracting IOP-related biomechanical stress and maintaining retina homeostasis. This is achieved through their ability to remove cellular debris and increased phagocytic activity in glaucoma onset and progression [49].

Although astrocytes continue to remain enigmatic in terms of retinal functions, they share common features with microglia, such as plasticity and the ability to change their phenotype toward either neurodegenerative or neuroprotective states under pathological conditions, as well as reactivity and ability to migrate to injury sites, as demonstrated by several studies [50–53]. Morphological changes in astroglia populations are classically recognized as key markers of reactive astrogliosis, which is also characterized by a strong upregulation of GFAP [54,55]. Among the first to link glaucomatous conditions to the inflammatory insults, Stevens *et al*. [54] demonstrated that retinal astrocytes become reactive and increase the complement component 1q (C1q) expression in RGCs, contributing to the glaucoma inflammatory-related degeneration and vision loss [54].

Astrocytes and microglia do not function independently in healthy or pathological tissue; rather, they team up to drive and intensify neuroinflammation [20,56]. A mutual communication between microglia and astrocytes has been well demonstrated during the onset, progression and amplification of the glaucomatous neuroinflammation [20,56–58]. This teamwork arises from both direct molecular interactions and their shared responses to environmental cues. In glaucoma, stress from increased IOP and damage to RGCs seem to be the key triggers that synchronize the astrocyte–microglia partnership. In addition to their close relationship, the molecules produced by these glial cells can also recruit immune cells from the bloodstream, further fueling neuroinflammation [15].

Astrocytes and microglia communicate with each other through different mechanisms. First, both cell types can sense and respond to the same signals at the same time. They have similar immune receptors that enable them to communicate and work together during inflammation. These cells can detect stress in other cells by recognizing damage signals. Both cells respond to ATP, which is released from stressed or dying RGCs. This ATP triggers inflammation through purinergic signaling. Besides purinergic receptors (e.g., ionotropic P2X7R-P2X purinoceptor 7), astrocytes and microglia also express pattern recognition receptor (PRR)-like toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). When these receptors are activated by damage signals, they can quickly trigger an inflammatory response [59].

Astrocytes and microglia crosstalk can either increase or decrease their responses. They do this by releasing molecules like cytokines, chemokines, or complement molecules. Astrocytes mainly produce chemokines, which bind to receptors on microglia and help microglia migration. Cytokines from astrocytes can also assist microglia in removing synapses. Complement components, like C3 from astrocytes, can support microglia with their eating function. Astrocytes and microglia also keep their numbers balanced. Microglia can control astrocyte numbers by phagocytosing them in the retina.

Communication between astrocytes and microglia can also affect their behavior. Congruently, microglia can induce astrocytes to become harmful, thus promoting inflammation [27]. In glaucoma, microglia can shift astrocytes from a protective anti-inflammatory A2 state to a harmful pro-inflammatory A1 state [27,60]. Interleukin-1alpha (IL-1α), tumor necrosis factor alpha (TNF-α) and C1q released by microglia support this phenotypic change. Accordingly, the genetic knockout of IL-1, TNF-α and C1q in mice model with IOP shows a reduction of harmful changes in retinal astrocytes [60].

Müller cells are a type of glial cell found only in the retina, stretching throughout its full thickness. Müller cells are strategically positioned transversely across all nuclear and plexiform layers, with their endfeet making contact with the vitreous cavity and their microvilli extending into the subretinal space. Within the IPL and OPL, these processes envelop synapses and form connections with blood vessels [61]. These cells play a crucial role in directing light to photoreceptors and in mitigating mechanical stress within the retinal tissue. They are classically identified by the expression of glutamine synthetase (GS), cellular retinaldehyde acid-binding protein (CRALBP), glutamate–aspartate transporter (GLAST), S100b and vimentin. Müller cells' soma is located in the inner nuclear layer (INL), with its processes extending in both directions towards the inner and outer retinal layers [62]. Although classically used as a marker of astrocytes, GFAP has been shown to be highly expressed by reactive Müller cells in glaucoma patients [63].

In detail, Müller cells play a crucial role in the rapid clearance of excess glutamate from the extracellular environment via amino acid transporters, particularly excitatory amino acid transporters. This process is essential for maintaining low glutamate levels, thereby preventing excitotoxicity. The conversion of glutamate to glutamine is facilitated by the enzyme glutamine synthetase, which is specifically expressed by Müller cells. Glutamine then acts as a precursor for the synthesis of glutamate in neurons. In glaucoma, both in human patients and in animal models, an increase in the expression of glutamine within Müller glia has been observed, suggesting a heightened activation of the glutamate–glutamine cycle. It is proposed that the rise in glutamine concentrations within Müller glia could be attributed to a diminished need for glutamine in injured RGCs. Beyond their function in clearing excess glutamate from the synaptic cleft, Müller glia are also capable of metabolizing glutamate as a substrate [64].

This support is vital for the survival of photoreceptors and neurons, as it enables the efficient uptake and recycling of neurotransmitters and their precursors, thereby ensuring precise neuronal communication [65].

Under stress conditions, Müller cells show cellular hypertrophy, which involves the thickening of both their somas and processes. This condition is also associated with increased cellular proliferation and an upregulation of cytoskeletal proteins, such as vimentin and a reduction in the expression of GS [66]. Similar to microglia and astrocytes, Müller cells initially display neuroprotective phenotypes through the release of factors such as pigment epithelium-derived factor (PEDF) or vascular endothelial growth factor (VEGF). However, they can also fuel neuroinflammation by releasing IL-1β, TNF-α, IL-6, complement protein C1q and NO expression that induce RGC loss when overstimulated. In glaucoma, Müller cells can play a role in neuroinflammation by expressing monocyte chemoattractant protein-1 (MCP-1), a chemokine that recruits monocytes and macrophages. If chronic and not promptly resolved, this recruitment leads to a sustained inflammatory response that contributes to RGCs' death [11,67]. Müller glia cells, activated in response to glaucoma, play a crucial role in preserving the integrity and homeostasis of neuronal tissue. This process involves the upregulation of receptors that are crucial for neuronal growth and survival, enhanced uptake of extracellular glutamate to shield RGCs from excitotoxic damage, and the release of nerve growth factor (NGF) [68].

Although Müller glia are more numerous than astrocytes in the retinal environment, both macroglial subtypes exhibit a range of shared functions alongside distinct attributes, many of which remain to be elucidated. Moreover, timing and site of macroglial activation are crucial to induce different activation states and to determine the beneficial or detrimental effect, thus making it more difficult to choose an appropriate therapeutic approach [69,70]. It is imperative for forthcoming research to explore both the unique and common roles of astrocytes and Müller glia. Furthermore, understanding their potential collaborative interactions is vital for gaining a comprehensive insight into their functions.

Generally, in the glaucomatous retina, proinflammatory cytokines play a crucial role in both microglia and macroglia. Although microglia act as primary responders to neural damage, initiating an inflammatory response that leads to neuronal loss, macroglia provide essential structural and metabolic support to neurons but can become reactive under chronic stress, contributing to neuroinflammation and to the RGC degeneration. Within this context, the involvement of the NF-κB signaling pathway attracts attention, being considered a central hub for neuroinflammation as well as for neuroprotection.

3. NF-κB Pathway in the Glial Retina Cells

The nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) transcription factor proteins are pivotal regulators of cell growth, differentiation, apoptosis [71,72], immune responses, inflammation and tumor initiation and progression, both in vertebrates and invertebrates [73,74]. NF-κB was initially identified as a nuclear factor in B cells that binds the enhancer element controlling immunoglobulin κ light chain expression [75]. Later, NF-κB binding sites were identified in the promoter site of genes that encode inflammatory cytokines and chemokines, major histocompatibility complex molecules, cell adhesion molecules, growth factors and regulators of apoptosis in various cell types [76]. Various stimuli, like bacterial or viral antigens, cytokines and growth factors (e.g., members of the TNF receptor superfamily or toll-like receptors), can activate NF-κB, leading to the transcriptional upregulation of inflammatory cytokines. Structurally, the Rel/NF-κB transcription factor family consists of several homo and heterodimeric complexes that bind to 9–10 base pair DNA sequences known as κB sites [77]. The NF-κB family includes five transcription factor proteins—NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), RelB and c-Rel—which can dimerize to form all possible combinations of homo and heterodimers. The prototypical form of NF-κB is the heterodimeric p50/p65 complex [78]. All NF-κB proteins are characterized by the presence of an N-terminal Rel homology domain (RHD), which is involved in DNA binding, dimerization process, nuclear localization and IκB inhibitor binding. RelA (p65), RelB and c-Rel contain a C-terminal transactivation domain (TAD) that enables them to activate target genes. p50 (p105 precursor) and p52 (p100precursor) possess a long ankyrin repeat—containing domain (ARD) at their C-terminus instead of the TAD domain—and therefore cannot activate target gene expression as a homodimer [79]. The activity of NF-κB is tightly regulated by its interaction with inhibitory IκB proteins. In unstimulated cells, NF-κB dimers are retained in an inactive form in the cytosol through their binding to IκB proteins. All IκBs recognize NF-κB via their ARD. Family members of IκB can be divided into three subgroups based on their function and structure: (1) classical IκB proteins (IκBα, IκBβ and IκBε); (2) NF-κB precursor proteins (p100 and p105); and (3) the nuclear IκBs (IκBζ, Bcl-3 and IκBNS) [80,81]. IκBα, IκBβ and IκBε are the main inhibitors of NF-κB dimers (p50/p65 and p65/p65) activation. The ARD of these proteins includes six repetitions of ankyrin; the SRD region contains conserved serine-rich sites that are phosphorylated by the IκB kinase complex (IKK), and lysine residues that are polyubiquitinated before proteolytic degradation [82]. p105 and p100 play a dual role in cells, are both precursors required for the maturation of p50 and p52 subunits of NF-κB and are both nonspecific inhibitors of NF-κB. IκBζ, Bcl-3 and IκBNS have nuclear localization signal (NLS) and are therefore in the nucleus. Bcl-3 interacts with homodimers of NF-κB p50 and p52, and can act either as an activator or as a repressor of transcription [83].

Various exogenous signals, such as proinflammatory cytokines (e.g., IL-1β and TNF-α), constituents of cellular pathogens (e.g., LPS) and radiation can induce activation of NF-κB. These signals induce the activation of a specific IκB kinase termed IKK. There are two pathways leading to the activation of NF-κB: the canonical and non-canonical pathways or the classical and alternative pathways, respectively. Pro-inflammatory cytokines (IL-1 and TNFα), components of bacterial cell walls (LPS), viruses and agents that damage DNA induce the canonical pathway through activation of the IKK $\alpha/\beta/\gamma$ complex present in the cytoplasm. The IKK complex consists of two catalytic subunits, IKKα and IKKβ, as well as a regulatory subunit, NEMO (IKKγ). The IKK complex consists of a homo- ($\alpha\cdot\alpha$ or $\beta\cdot\beta$) or heterodimer ($\alpha\cdot\beta$) associated stoichiometrically with NEMO [84]. The catalytic subunits

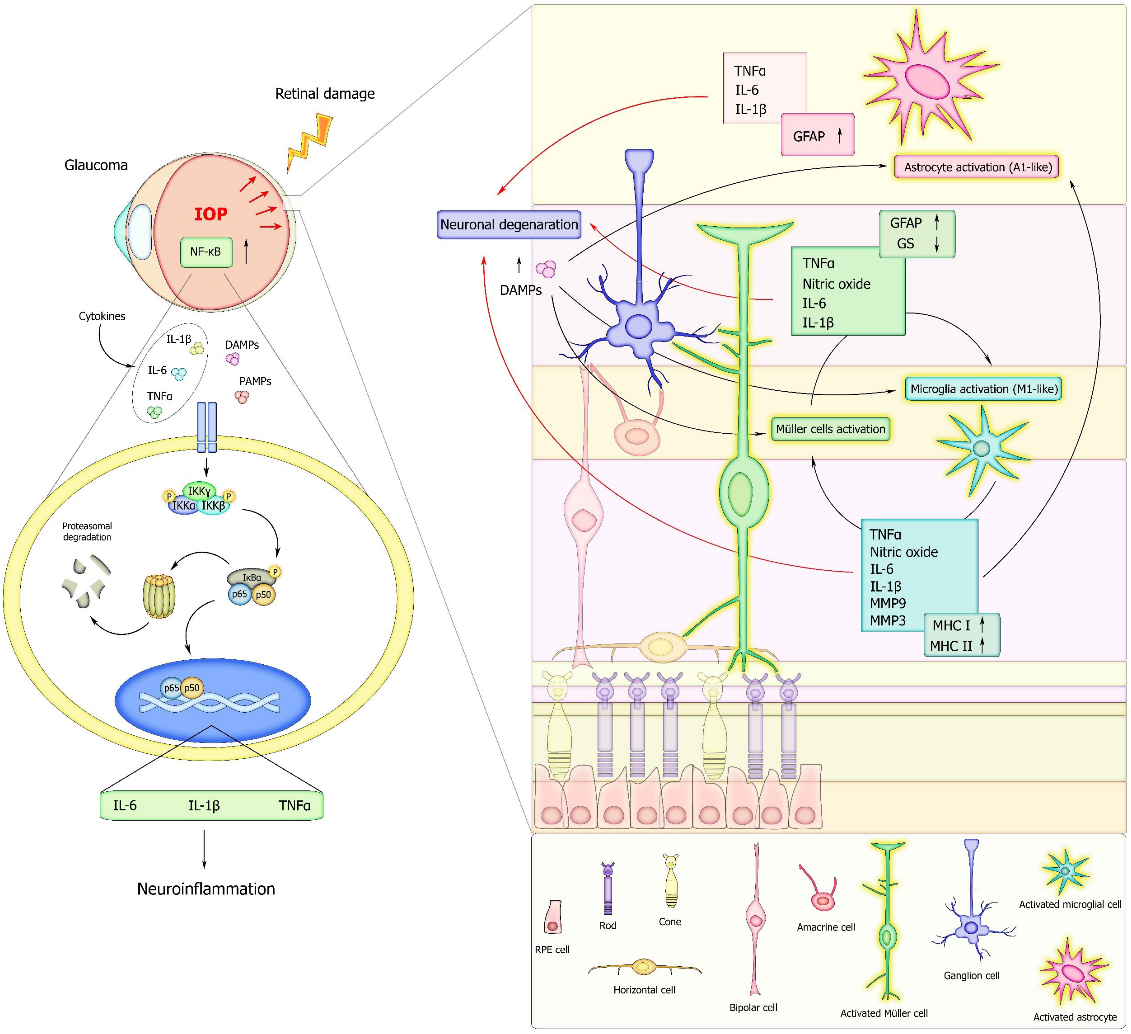

Fig. 2. Schematic representation of the NF-κB canonical pathway involvement in the glaucomatous glial cells. NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; OLM, outer limiting membrane; PL, photoreceptor layer; RPE, retinal pigment epithelium; DAMPs, damage-associated molecular patterns; GFAP, glial fibrillary acidic protein; GS, glutamine synthetase; PAMPs, pathogen-associated molecular patterns; MMP9 and MMP3, matrix metalloproteinases.

IKKα and IKKβ share about 50% sequence identity and show an N-terminal kinase domain and "leucine zipper" and "basic helix-loop-helix" regions, while IKKγ has a helical structure interrupted by "coiled-coil" structures and a C-terminal leucine-zipper (LZ) motif [85]. IKK activation leads to the phosphorylation of two serine residues (Ser-32 and Ser-36) of the IκB inhibitor. Phosphorylation of IκB, in turn, leads to Lys48-linked polyubiquitination, which targets IκB for degradation by the 26S proteasome. At this point, NF-κB is free and can translocate into the nucleus [86], where they activate specific target gene expression involved in inflammatory response, cell survival, immune response and apoptosis. The alternative pathway is induced by LT-β (Lymphotoxin beta) and BAFF (B-cell Activating Factor). Ligand binding to their respective receptors leads to activation of the NF-κB-inducing kinase (NIK), which phosphorylates and activates an IKKα complex. This complex, in turn, phosphorylates two serine residues adjacent to the ankyrin repeat C-terminal IκB domain of p100, leading to its partial proteolysis and liberation of the p52/RelB complex; this alternative pathway is primarily involved in the activation of p100/RelB complexes during B-and T-cell organ development [87]. The IKK activation process is coupled with a negative feedback control mechanism that quickly modulates NF-κB activity. The genes coding for some IκB isoforms show binding-sites for NF-κB in their promoter, allowing NF-κB to self-regulate its own activity through transcriptional induction of its inhibitors [88]. Genetic alterations targeting components of the NF-κB family, as well as dysfunction within the NF-κB signaling pathway, have been associated with neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease

(AD), as well as in glaucoma [89]. *In silico* and *in vivo* studies demonstrated that NF-κB activation is triggered by α-sinuclein and amyloid-β in PD, AD and glaucoma. In addition, several studies demonstrated that microglia activation and neuroinflammatory processes are involved in these neurodegenerative diseases [16,90]. In detail, recently Li *et al.* [9] using a transcriptomic approach, identified insulin-like growth factor-binding protein-like protein 1 (IGFBPL1), able to switch molecular signatures of activated microglia via the NF-κB pathway in mice model of neuropathies [91]. These findings suggest that AD, PD and glaucoma could share a common mechanistic pathogenic process that could be considered potentially as an attractive target for neurodegenerative disorders [91–95]. Although NF-κB is also involved in IOP regulation through toll-like receptor 4 (TLR4) at the level of the trabecular meshwork [96], this signaling plays a crucial role in response to IOP and subsequent mechanical stress. Wang *et al.* [97] showed that suppression of TLR4/NF-κB in activated rat microglia following mechanical injury leads to a reduction of pro-inflammatory cytokine expression. Again, astrocytes sense IOP through mechanosensitive ion channels and release ATP [98], which, in turn, mediates microglia's inflammatory response via P2X7R/Ca^{2+}/NFAT/NF-κB pathway [18]. NF-κB also regulates the response to S100B protein, which is expressed by both astrocytes and microglia. Higher doses of S100B are able to activate astrocytes and microglia, promoting the expression of inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines via NF-κB [99,100]. Moreover, rats immunization with S100B activates NF-κB and cytokine production, leading to a glaucomatous condition in autoimmune glaucoma models [101]. As previously discussed, microglia and macroglia polarization could shape the neuroinflammatory status of the glaucomatous retina. The existing cross-talks between these glial cells suggest that NF-κB-regulated pro-inflammatory cytokines produced in astrocytes may also play a role in modulating the inflammatory responses of microglia [102]. Furthermore, a variety of pro-inflammatory cytokines and chemokines, which are associated with glial upregulation in glaucoma, including TNF-α, IFNγ, IL-1, IL-2, IL-12, IL-17, FasL and iNOS, have been identified as target genes of NF-κB (Fig. 2) (Table 1, Ref. [18,61,97,99–106]) [59,107].

Inhibition of NF-κB activation through the cre/lox-based conditional deletion of astroglial p65 led to a reduction in the production of pro-inflammatory cytokines in experimental mouse models of glaucoma [102]. Notably, in addition to the diminished inflammatory activity of astroglia, alterations in microglial responses were also observed following p65 deletion in GFAP-expressing astroglia. The pro-inflammatory response of microglia was significantly reduced in ocular hypertensive GFAP/p65 mice compared to ocular hypertensive $p65^{f/f}$ controls. These preliminary findings suggest that, similar to the modulation of astrocyte responses by microglia, astrocytes—through NF-κB-regulated mediators—can influence microglial responses, thereby exacerbating neuroinflammation [27].

Recent research focusing on the transcriptomic and proteomic profiling of human donor eyes and animal models affected by glaucoma has identified an early increase in the expression of numerous molecules and pathways involved in inflammatory signaling, such as pattern recognition receptors, TLRs, NLRs, Myeloid Differentiation Primary Response 88 (MyD88), Mitogen-Activated Protein Kinases (MAPKs) and NF-κB [40,103,108]. Furthermore, in glaucoma, it is widely accepted that neuroinflammation driven by glial cells involves multiple pathways, such as TNFR (Tumor Necrosis Factor receptor) signaling, TLR signaling and the inflammasome, all of which are predominantly regulated by NF-κB. Upon encountering environmental signals, TNFR and TLR signaling pathways initiate the transcriptional priming of the inflammasome through the activation of NF-κB. This activation enhances the expression of inflammasome components and the precursors of cytokines activated by the inflammasome, including IL-1β [109].

In an experimental glaucoma model, the conditional deletion of IκKβ in astroglia expressing GFAP (GFAP/IκKβ) using the cre/lox system led to a reduction in the production of pro-inflammatory cytokines, which are transcriptional targets of NF-κB, including TNF-α, IFNγ, IL-1 and IL-2. By inhibiting the NF-κB-regulated inflammatory functions of astroglia, structural and functional protection was afforded to RGCs in eyes with ocular hypertension [102].

Lebrun-Julien and colleagues [110] demonstrated that the activation of the NF-κB signaling pathway, along with the upregulation of NGF expression, leads to the induction of TNF-α expression by Müller cells, thereby contributing to neurotoxicity *in vivo*.

Targeting the NF-κB pathway presents promising therapeutic strategies for mitigating glaucoma-related damage. However, due mainly to the systemic dysfunction related to NF-κB inhibition, few attempts have been made. Initial approaches aiming at inhibiting the NF-κB signaling pathway using specific inhibitors could reduce inflammation and subsequently the progression of glaucoma. NF-κB inhibitors (e.g., Resveratrol, Pycnogenol) are already being explored for their benefits in various other inflammatory and neoplastic diseases, due to their ability to suppress pro-inflammatory cytokines and protect against tissue damage [111,112]. Ouyang and colleagues [113] employed a multifunctional nanosystem that co-delivers NF-κB inhibitors with other therapeutic agents to enhance treatment efficacy. For instance, a system combining an NF-κB inhibitor like thalidomide with an activator of the Nrf2 pathway has shown promise in reducing inflammatory responses and promoting recovery in inflammatory diseases

Table 1. NF-κB pathway involvement in glial and other retinal cells.

NF-κB PATHWAY IN GLIAL CELLS

Functions	Cell type	Cytokines	Receptors	Diseases	Model	Refs
Neuroinflammation	Müller glia, Microglia, Astrocytes	TNF-α, IL-16, IL-6, IL-4, IL-10, CCL2, IL-1β, TGF-β, IFN-γ	CD44, TLR, TNFR1, P2X7R, TLR4, IL-1R	Glaucoma, Retinitis pigmentosa	*In vitro, In vivo, Ex vivo*	[18,61,97,103]
Neuroinflammation, neurodegeneration	Müller glia, Microglia, Astrocytes	TNF-α, IL-1β, HMGB1, CNTF, IL-6, IL-1α, IL-2, IL-10, IL-12, IL-13, IL-17, IFN-γ	TLR, CNTFR, CD44, TRPV4, TNFR1	Glaucoma, Hypertensive Retinopathy	*In vitro, In vivo, Ex vivo*	[102,104,106]
Glial reactivity, neurodegeneration	Müller glia, Microglia	TNF-α, IL-1β, IL-6, OPN	TNFR, IL-1R1, TLR, CD44, RAGE	Glaucoma, Neurodegenerative disease	*In vitro, In vivo, Ex vivo*	[100,105]
Oxidative and neurotoxic response	Astrocytes	TNF-α, IL-1β	RAGE	Glaucoma, Neurodegenerative disease	*In vitro*	[99,102]
Cell survival	Microglia, Astrocytes	IL-1α	p75	Glaucoma	*In vitro*	[102]

NF-κB PATHWAY IN OTHER RETINAL CELLS

Functions	Cell type	Cytokines	Receptors	Diseases	Model	Refs
Neuroinflammation, neurodegeneration	RGC	TNF-α, IL-1β, IL-6	TRPV4, TNFR1	Glaucoma	*In vitro, In vivo*	[104]
Neurodegeneration	RGC, Optic nerve	IL-1β	TLR4	Glaucoma	*In vitro, Ex vivo*	[101]

CNTF, ciliary neurotrophic factor; TRPV4, transient receptor potential vanilloid 4; HMGB1, High Mobility Group Box 1; OPN, Optineurin; CD44, Cluster of Differentiation 44; TNFR1, Tumor Necrosis Factor Receptor 1; P2X7R, P2X purinoceptor 7; CNTFR, Ciliary Neurotrophic Factor Receptor; RAGE, Receptor for Advanced Glycation Endproducts.

[113]. Compounds like parthenolide have demonstrated a strong NF-κB inhibition along with anti-inflammatory and anti-cancer activities. Such natural compounds may offer a less toxic alternative for the long-term management of inflammatory responses in glaucoma [112]. Implementing chronic therapeutic schemes using specific NF-κB inhibitors could be beneficial in maintaining long-term therapeutic effects without significant adverse reactions. This strategy could potentially halt or slow down disease progression, preserving vision [114]. However, although inhibition of NF-κB represents a promising therapeutic approach, the use of core pathway NF-κB inhibitors could be detrimental in some contexts. For example, although S100B protein supports inflammation in astrocytes and microglia via NF-κB, the inhibition of this signaling could have a negative effect on neurons in which S100B promotes NF-κB-dependent neuronal survival [115]. Overall, these aspects impose the identification of more specific downstream NF-κB effectors and the development of highly specific inhibitor molecules. The activation of NF-κB signaling in Müller cells occurs rapidly following retinal injury, suggesting its importance as an early response mechanism. Moreover, Müller cells respond to IOP through pressure-sensitive transient receptor potential vanilloid 4 (TRPV4) that increases TNF-α expression and induces gliosis via JAK2/STAT3/NF-κB signaling [104] and statins are able to mitigate gliosis by inhibiting NF-κB activation. Interestingly, this activation is not autonomous but depends on signals from reactive microglia. This intercellular communication underscores the intricate network of cellular interactions that orchestrate the retinal response to injury. Researchers have explored various approaches to modulate NF-κB signaling in Müller cells, aiming to enhance the regenerative potential of the retina. Inhibition of NF-κB signaling, achieved through either pharmacological interventions or genetic knockout techniques, has shown promising results. When combined with the overexpression of Achaete-Scute Family BHLH Transcription Factor 1 (Ascl1), a transcription factor known to promote neuronal differentiation, NF-κB inhibition significantly enhances the ability of Müller cells to reprogram into neurons. This finding suggests that NF-κB signaling acts as a barrier to neurogenic reprogramming and that its suppression can unlock the regenerative potential of Müller cells. The role of NF-κB in maintaining glial identity and suppressing neurogenic potential is not isolated but involves coordination with other signaling pathways and transcription factors. For instance, NF-κB interacts with the TGFβ/Smad3 pathway, known for its involvement in cell growth and differentiation [105]. Additionally, NF-κB works in concert with transcription factors such as Id proteins, which are important regulators of cell fate decisions. This complex network of interactions ensures the maintenance of glial identity and functions under normal conditions. Following retinal injury, NF-κB signaling in Müller cells promotes the expression of inflammatory gene networks. This pro-inflammatory response contributes to the overall glial reactivity observed in the damaged retina. By driving these inflammatory and reactive processes, NF-κB signaling acts as a key regulator that pushes Müller cells towards restoring quiescence rather than undergoing neurogenic reprogramming. This tendency to return to a quiescent state, rather than initiating a regenerative program, is a characteristic feature of mammalian retinal response to injury, contrasting with the robust regenerative capabilities observed in some non-mammalian vertebrates [106]. Understanding the role of NF-κB signaling in Müller cells provides valuable insights into the limitations of mammalian retinal regeneration and offers potential targets for therapeutic interventions. By modulating NF-κB activity and its associated pathways, researchers may be able to enhance the regenerative capacity of the mammalian retina, potentially leading to novel treatments for retinal injuries and degenerative diseases. These strategies focusing on NF-κB may provide a multifaceted approach to managing glaucoma by emphasizing inflammation reduction, which is a critical factor in protecting the optic nerve and maintaining vision. The inflammatory cascade initiated by NF-κB activation in glial cells can have far-reaching effects on the retinal microenvironment. For instance, the release of MMPs by activated glial cells can lead to the remodeling of the extracellular matrix, potentially altering the structural integrity of the retina and optic nerve head. This remodeling process may contribute to the characteristic cupping of the optic disc observed in glaucoma patients. However, NF-κB activation in glial cells also has potential neuroprotective effects. It induces the upregulation of antioxidant enzymes (superoxide dismutase (SOD) and catalase (CAT)), which help neutralize reactive oxygen species and protect against oxidative damage, and anti-apoptotic factors (B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL), and Growth Arrest and DNA Damage-inducible beta (GADD45β)), which may help prevent retinal ganglion cell death in glaucoma. NF-κB activation can also stimulate the production of neurotrophic factors, such as BDNF and CNTF, which support the survival and function of retinal neurons, and modulate glutamate uptake and metabolism, helping to maintain proper neurotransmitter homeostasis and protect against excitotoxicity. This dual nature of NF-κB signaling in glial cells highlights the complex interplay between neuroprotection and neurodegeneration in glaucoma. The balance between these opposing effects may depend on various factors, including the severity and duration of the glaucomatous insult, the specific glial cell types involved and the overall retinal microenvironment (Fig. 3).

4. Conclusions

Reported evidence suggests that NF-κB could also play a relevant role in the context of glaucoma pathogenesis, and in particular, regulating inflammatory response and

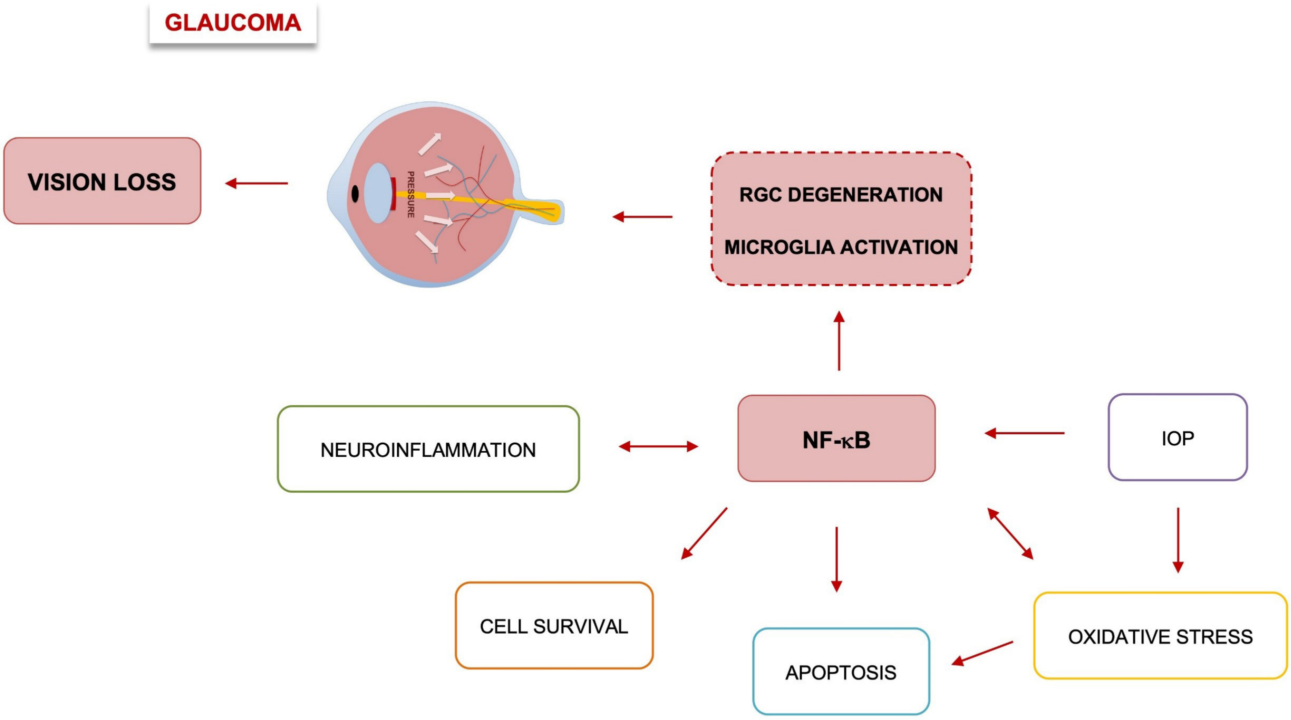

Fig. 3. Role of NF-κB signaling pathway in glaucoma. IOP, intraocular pressure; RGC, retinal ganglion cell.

cell survival pathways within retinal glial cells. The current prevalent pathologic interpretation of glaucoma supposes the etiologic role of elevated intraocular pressure leading to mechanical stress on retinal tissues. However, the reactive phenotype of resident cells in response to mechanical stress, and in particular of glial cells, could contribute in a clinically relevant manner to the pathogenesis of this disease. Indeed, glial cells—including astrocytes, Müller cells and microglia—are essential for maintaining retinal homeostasis and supporting neuronal function. These cells form a complex network that provides structural, metabolic and functional support to retinal neurons, including retinal RGCs.

A clear pathologic description centered on NF-κB in the context of ocular diseases is not yet completely achievable. One hurdle is represented by the fact that specific genes targeted by NF-κB can vary depending on the cell type and the nature of the activating stimulus. For example, in Müller cells, NF-κB activation promotes the release of neuroprotective factors such as BDNF and CNTF, which support the survival and function of retinal neurons, particularly in response to stress or injury. Conversely, in microglia, NF-κB activation stimulates the production of pro-inflammatory mediators, including cytokines TNF-α and IL-1β, which, while beneficial for pathogen or damaged cells clearance, may promote chronic inflammation and tissue damage if sustained. In addition to cytokine production, activated microglia can also release reactive oxygen species, proteases and other factors that can modulate the retinal microenvironment and influence the behavior of neighboring cells. Astrocytes also respond to NF-κB activation. In these cells, NF-κB signaling modulates the expression of genes involved in antioxidant defense, glutamate uptake and the production of extracellular matrix components, all critical processes for maintaining the blood–retinal barrier and regulating neurotransmitter levels in the retinal microenvironment. Astrocytes also play a key role in supporting retinal vasculature and regulating blood flow, both essential for maintaining proper oxygenation and nutrient supply to retinal neurons.

Understanding these molecular dynamics is crucial for developing targeted therapies aimed at mitigating glaucomatous damage and preserving vision. Research in this area may lead to the development of novel therapeutic approaches that modulate NF-κB activity in glial cells to promote neuroprotection while minimizing harmful inflammatory responses. Such strategies could include the use of selective NF-κB inhibitors, targeted delivery of anti-inflammatory agents to retinal glial cells, or the development of therapies that enhance the neuroprotective aspects of NF-κB signaling while suppressing its pro-inflammatory effects. In particular, reliable methods for cell-type-specific NF-κB inhibition, which would allow targeting only the disease-involved cells while sparing healthy ones, are particularly needed, enabling at the same time a mitigation of adverse effects, and enhancing therapeutic potential. These approaches could complement existing glaucoma treatments, which primarily focus on reducing intraocular pressure, by addressing the underlying cellular and molecular mechanisms of the disease. Future research directions in this field may also include the development of advanced imaging techniques to detect NF-κB activation in specific glial cell populations *in vivo*, allowing for real-time monitoring of glial responses in glaucoma patients. Additionally, the use of single-cell transcriptomics and proteomics could provide valuable insights into the heterogeneity of glial cell responses and help to identify specific cellular subpopulations that may be particularly important in mediating neuroprotection or neurodegeneration.

In summary, the role of NF-κB signaling in retinal glial cells represents a complex and multifaceted aspect of glaucoma pathophysiology. By unraveling the intricacies of this signaling pathway and its effects on glial cell function, researchers and clinicians may be able to develop more effective and targeted treatments for glaucoma, ultimately improving the outcomes of patients affected by this sight-threatening disease.

Author Contributions

FV and MDVN drafting the manuscript prepared the figure and performed bibliographic search. IF, FDA, FDG and DVer performed bibliographic search and formatting; DC, AA, EA gives a fundamental contributes to the design of the study and also support the revision process. DVec and FZ conceived the project and reviewed the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Search Methodology is provided in the supplementary materials. Supplementary material associated with this article can be found in the online version, at https://doi.org/10.31083/FBL45644.

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