REVIEW ARTICLE

Contribution of TNF-α to the development of retinal neurodegenerative disorders

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ABSTRACT. During the late 1970s, tumor necrosis factor alpha (TNF-α) was initially recognized as an endotoxin-induced substance that was mainly produced by macrophages, and able to cause the lysis of certain tumor cells. Subsequent research demonstrated that TNF-α mediates a broad range of cellular activities, including proliferation, survival, differentiation and apoptosis. It is also considered to be essential for the induction and maintenance of the inflammatory immune responses. Meanwhile, visual impairment imposes a substantial disease burden on society. It is associated with both significant economic impact and reduction in quality of life. Visual impairment raises serious social challenges for both patients and their families, interfering with day-to-day life, and can limit employment possibilities. Many of the most common, irreversible blinding pathologies involve neuronal loss from the retina, which is the light-sensing tissue of the eye. The retina, being part of the central nervous system, is unable to regenerate neurons lost to disease. Therefore, in the current review we will discuss the association between increased expression of TNF-α with neurodegenerative disorders, downstream cellular signaling mechanisms following interaction of TNF-α with its receptors, and the role of TNF-α as a possible target in the treatment of retinal neurodegenerative disorders.

Key words: TNF-α, neurodegenerative disorders, age-related macular degeneration, retinitis pigmentosa, glaucoma, ischemic retinopathy

Abbreviations

AMD:	age-related macular degeneration
AP-1:	activator protein-1
CNS:	central nervous system
ERK:	extracellular signal-regulated kinases
FADD:	Fas-associated death domain protein
ET:	endothelin
IOP:	intraocular pressure
IR:	ischemic retinopathy
JNK:	c-Jun N-terminal kinase
MAPK:	mitogen-activated protein kinases
NFκB:	nuclear factor kappa B
NMDA:	N-methyl-d-aspartate
proNGF:	pro-nerve growth factor
RGCs:	retinal ganglion cells
RIP1:	receptor-interacting protein 1
RP:	retinitis pigmentosa
RPE:	retinal pigment epithelium
SP-1:	specificity protein-1
TACE :	TNF-α cleaving enzyme
TNF-R:	tumor necrosis factor receptor
TNF-α:	tumor necrosis factor-α
TRADD:	TNF-R1-associated death domain protein
TRAF2:	TNF-receptor-associated factor 2

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Tumor necrosis factor (TNF)-α was first described by Carswell and colleagues in 1975 as a proteinaceous component of serum from bacterially-challenged mice. It was shown to induce the death of cancer cell lines *in vitro* and eliminate transplanted sarcomas *in vivo* [1]. Subsequent research demonstrated that TNF-α mediates a broad range of cellular activities, including proliferation, survival, differentiation and apoptosis, and is considered to be essential for the induction and maintenance of the inflammatory immune response [2]. Subsequent molecular isolation and characterization of the TNF-α gene indicated that it is a 212-amino acid protein that is localized to the cell surface in a pro-form and produced by lymphoid cells, mast cells, endothelial cells, fibroblasts and glial cells [3].

TNF-α interacts with two cognate receptors: p55 (TNF-R1) and p75 (TNF-R2), which are expressed on neurons, astrocytes and microglia throughout the central nervous system (CNS). Only TNF-R1 contains a cytoplasmic death domain and may directly induce apoptosis [4]. In the vast majority of cells, TNF-R1 appears to be the key mediator of TNF-α signaling [5]. There have been several reviews of the TNF-α receptor and its signaling pathway [4, 6, 7]. The mechanism of action of TNF-α is summarized in *figure 1*.

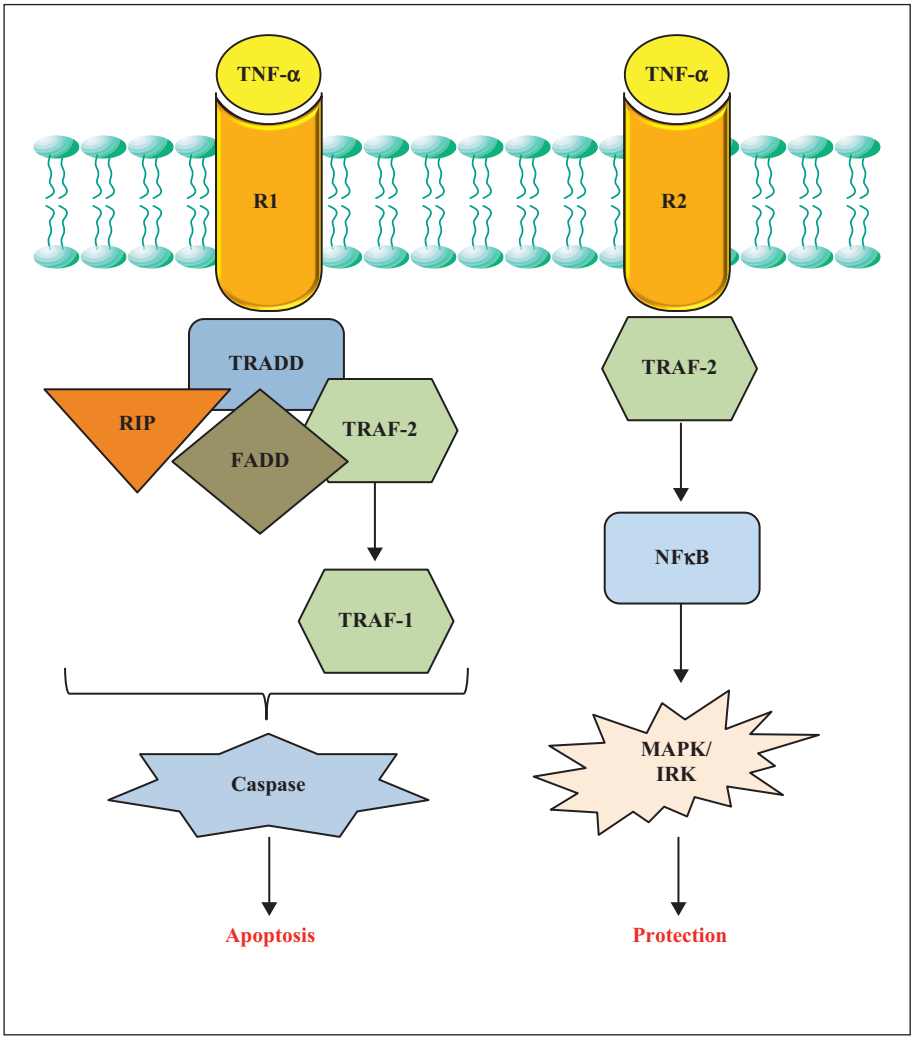

Figure 1

Schematic representation of the mechanism of action of TNF-α.
Binding of TNF-α to TNF-R1 and TNF-R2 induces receptor trimerization and recruitment of several signaling proteins to the cytoplasmic domains of the receptors. TNF-R1 activates the TNF-R1-associated death domain protein (TRADD), which serves as a platform to recruit at least three additional mediators, receptor-interacting protein 1 (RIP1), Fas-associated death domain protein (FADD) and TNF-receptor-associated factor 2 (TRAF2), which, in turn, recruits TRAF1 leading to activation of caspases. TNF-R1 activates TRAF2, leading to rapid activation of nuclear factor kappa B (NFκB), promoting cell survival.

Several TNF-α blockers have been developed and approved for treatment of many diseases. TNF-α blockers are summarized in *table 1*.

NECROTIZING EFFECT OF TNF-α

A number of studies have supported the contribution of TNF receptors to cytotoxicity [12, 13]. Picogram concentrations of TNF-α known to be non-cytotoxic, induce neuronal cell death through the silencing of survival signals [14]. Both tissue distribution of the TNF-α receptors and the differentiation state of the target cell influence the cellular response to TNF-α. Several mechanisms have been reported to be associated with the cytotoxic effect of TNF-α. It has been reported that TNF-α involves both caspase-dependent and caspase-independent components of the mitochondrial cell death pathway, and the generation of ROS [15]. TNF-α can modulate ion channel activity, thereby regulating neuronal excitability, synaptic plasticity, and excitotoxic injury [16]. In addition, similar to several pathological conditions that are largely dependent on excessive glutamate release and subsequent over-stimulation of the N-methyl-d-aspartate (NMDA) receptor, TNF-α release has been associated with glutamate excitoxicity [17]. TNF-α also activates matrix metalloproteinases, which are not only involved in tissue remodeling in the glaucomatous optic nerve head, but have also been associated with neurotoxicity [18]. Finally, TNF-α is a potent stimulator of endothelin (ET)-1, a potent vasoactive peptide, which can produce optic nerve damage, synthesis and secretion in several ocular cell types, including optic nerve head astrocytes [19].

EFFECTS OF TNF-α ON VASCULATURE INTEGRITY AND PERMEABILITY

TNF-α was named after its property to produce hemorrhagic necrosis in experimental tumors. Accumulating evidence suggests that TNF-α plays a pivotal role in the disruption of macrovascular and microvascular circulation both *in vivo* and *in vitro* [20]. TNF-α is known to affect tumor vessel destruction and improve vascular permeability. Several mechanisms have been postulated to explain how TNF-α destroys vasculature integrity. Firstly,

Table 1
TNF-α blockers:

TNF-α blocker	Type	Uses
Etanercept	Soluble TNF-receptor [8]	Treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis
Infliximab	Human IgG1 constant regions and murine variable regions [9]	Treatment of Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and may be effective in sarcoidosis
Adalimumab	Human IgG1 constant and variable regions [10]	Treatment of Crohn's disease, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
Golimumab	Human IgG1 constant and variable regions [10]	Treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
Certolizumab pegol	Humanised Fab' fragment [11]	Treatment of Crohn's disease and rheumatoid arthritis

membrane TNF-α can induce angiogenesis and it can synergize with VEGF to augment vascular permeability [21]. Secondly, TNF-α impairs ET-dependent and nitric oxide-mediated vasodilation in various vascular beds such as mouse coronary arterioles [22], rat coronary arterioles [23], cat carotid arteries [24] and bovine small coronary arteries [25]. Finally, TNF-α activates the transcription of NFκB, which regulates the expression of genes involved in inflammation, oxidative stress and endothelial dysfunction [26, 27]. TNF-α initiates the signaling cascades via the IKK [IκB (inhibitor of NF-κB) kinase] complex [28].

RETINAL NEURODEGENERATIVE DISORDERS

Although the retina, the light-sensitive tissue lining the inner surface of the eye, constitutes part of the CNS, it is a highly accessible tissue when compared with the brain. It is the only part of the CNS that can be visualized non-invasively. Like the brain, the retina is unable to regenerate neurons lost to disease. Visual impairment imposes a substantial disease burden on society as it can limit employment possibilities [29]. While some causes of visual impairment, for example, cataract, are reversible and readily treated, others, such as glaucoma and macular degeneration, are both common and often irreversible. Furthermore, many of these pathologies are associated with increased age and, therefore, are becoming increasingly prevalent in aging populations [30].

Retinal neurodegenerative diseases can be broadly divided into those that affect the outer retina and those that affect the inner retina. Outer retinal pathologies often result in the death of the photoreceptor. Very common outer retinal pathology includes age-related macular degeneration (AMD) [31] and retinitis pigmentosa (RP) [32]. Neurodegenerative diseases of the inner retina can affect both bipolar cells and retinal ganglion cells (RGCs), the loss of which disrupts the flow of information through the visual pathway. Most common inner neurodegenerative disorders include glaucoma [33] and ischemic retinopathy [34].

CONTRIBUTION OF TNF-α TO GLAUCOMA

Glaucoma refers to a group of conditions that together comprise the most common inner retinal neurodegenerative disease. It was reported to be affecting 60.5 million people in 2010, and predicted to rise to 79.6 million by 2020 [30]. Selective loss of RGCs is a hallmark of glaucoma, causing optic nerve degeneration and impairing the retinal connection to the brain. Glaucoma can be asymptomatic until significant visual field loss occurs, often before diagnosis. The major axes in the glaucoma pathogenic cascade are summarized in *figure 2*.

The correlation of TNF-α with glaucomatous changes has been established in human and animal *in vivo* studies that have shown that either serum or intraocular TNF-α levels are increased [35, 36]. TNF-α has been implicated as a mediator of RGC death in glaucomatous retina [17, 37]. Production and release of TNF-α occurs very early on following exposure to stresses such as elevated intraocular pressure (IOP) or ischemia. In addition, intravitreal injection of TNF-α in rats was found to induce axonal degeneration from two weeks to two months after injection, whereas significant RGC loss was noted at two months after injection [38]. TNF-α can also act as a downstream mediator of proapoptotic factors such as pro-nerve growth factor (proNGF) [39, 40]. Therefore, TNF-α not only acts as a direct mediator of RGC apoptosis, it can also be an upstream or downstream mediator of other proapoptotic factors.

The search for pharmacological agents in the treatment of glaucoma has placed greater emphasis on providing direct neuroprotection to RGCs. However, simple modulation of elevated IOP is not enough to prevent RGC loss. Interestingly, TNF-α has been widely recognized as an attractive therapeutic target. Although intravitreal injection of TNF-α in the mouse has been shown to induce degenerative changes in RGCs, similar changes were not induced in mice with the TNF-α gene deleted or immune depletion of TNF-α in wild-type mice [41, 42]. Tezel and Wax also showed that RGC apoptosis was attenuated by a neutralizing antibody against TNF-α [43]. Moreover, a dopaminergic and antiglaucoma drug, GLC756, has been recently shown to inhibit TNF-α release from activated rat mast cells and is suggested to have a potential beneficial effect in the management of glaucoma [44, 45]. In addition, calcium channel blockers such as verapamil have been shown to deactivate NMDA receptors and inhibit the release of TNF-α, making them potentially useful in the management of glaucoma and other retinal neurodegenerative disorders [17]. The usefulness of anti-TNF-α therapy in glaucoma will depend upon its ability to block selectively excessive TNF-α and TNF-R1 expression

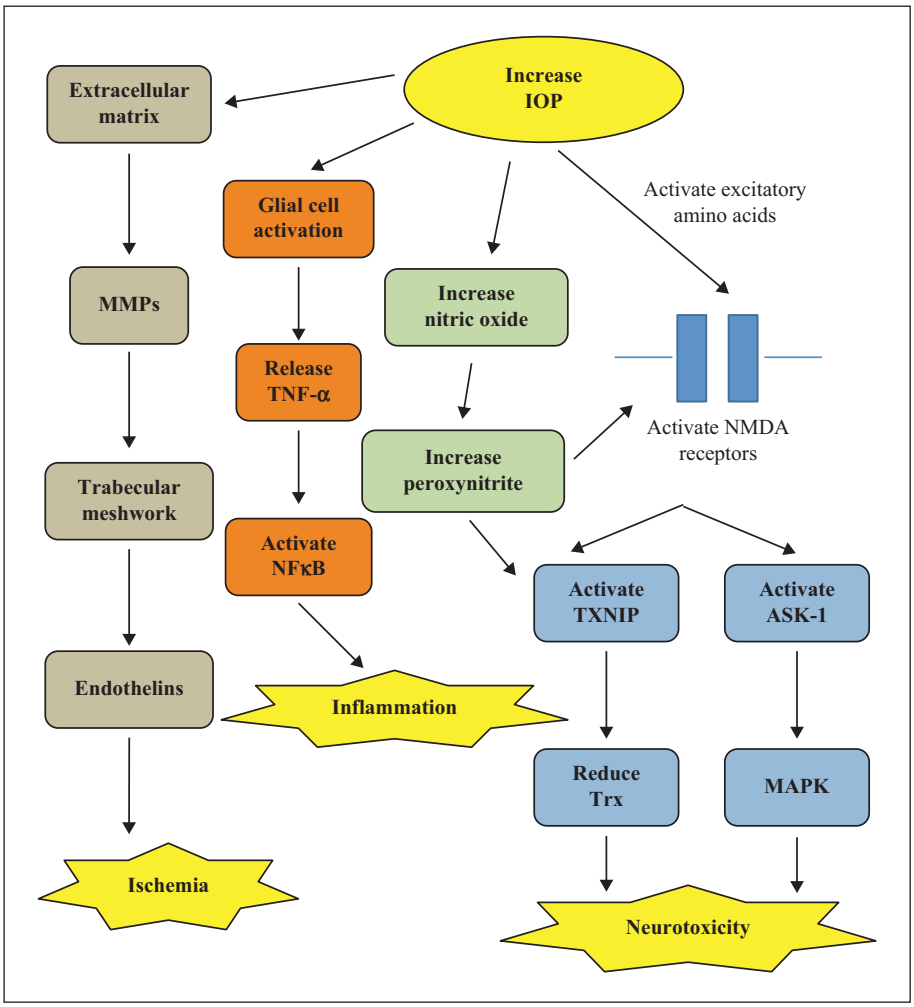

Figure 2

Major axes in the glaucoma pathogenic cascade. Trx: thioredoxin; TXNIP: thioredoxin interacting protein; ASK-1: apoptosis signal-regulating kinase 1; MAPK: mitogen-activated protein; MMPs: matrix metalloproteinase; NFκB: nuclear factor kappa B; NMDA: N-methyl-d-aspartate.

without significantly affecting its physiological functions such as local immunity. Moreover, the outcome of anti-TNF-α therapy may be influenced by several other, patient-related factors. A summary of the reports that demonstrated the use of TNF-α antagonists in the treatment of glaucoma is shown in *table 2*.

CONTRIBUTION OF TNF-α TO ISCHEMIC RETINOPATHY

Ischemic retinopathy (IR) develops when the retinal blood flow is insufficient to match the metabolic needs of the retina, the most highly demanding of any tissue [52]. IR is a potentially visually devastating disease that occurs in the middle-aged and the elderly. This condition is often referred to as a stroke of the optic nerve, and it usually begins suddenly, with little warning, in one eye, but frequently progresses to the other eye over time. Vision loss often includes both the loss of visual field and visual acuity, which can vary from being very slightly to severely impaired. Retinal ischemia plays a pivotal role in a number of retinal degenerative diseases such as diabetic retinopathy, retinopathy of prematurity and retinal artery occlusion [34, 53]. The major lines in the pathogenic cascade of ischemic retinopathy are summarized in *figure 3*.

Ischemia–reperfusion injury involves many signaling mechanisms that result in necrotic and apoptotic cell death [54]. A variety of substances, such as oxygen free radical, nitric oxide and proinflammatory cytokines, have been implicated in ischemic retinal injury [52]. However, recent studies have provided evidence that TNF-α plays a central role in the pathogenesis of a number of IR disorders [37, 55-57]. In previous studies, identification of the main source of TNF-α production under stress/ischemic conditions remained elusive. A variety of cell types, including activated macrophages, astrocytes, microglia and/or neuronal cells under stress/ischemic conditions have been proposed as responsible for the enhanced production of TNF-α. TNF-α acts upstream of the caspases and participates in ischemic neuronal injury [58].

Many studies have shown that the inhibition of TNF-α leads to protection in models of ischemia/reperfusion in rat brain, mouse brain and rat myocardium [59, 60]. In the eye, *in vivo* neutralization of TNF-α during retinal ischemia, significantly preserves inner retinal function [54]. Moreover, raising retinal cell cultures under ischemic conditions leads to massive RGC death; however, addition of TNF-α or TNF-R1 antibody to culture medium provides significant protection from cell death [61]. *Table 3* showed a summary of the reports that have studied the effect of TNF-α antagonists in the treatment of ischemic retinopathy.

Table 2
Summary of reports that examined the use of TNF-α antagonists in the treatment of glaucoma:

TNF-α inhibitor	Species	Summary	References
Etanercept	Rat	Blocking TNF-α activity inhibits the microglial response and prevents axonal degeneration and loss of RGCs in glaucoma.	[46]
Infliximab	Human	Infliximab resulted in better clinical responses with fewer ocular complications than etanercept in the treatment of glaucoma.	[47]
		Infliximab appears to be safe and effective in the treatment of secondary glaucoma	[48, 49]
	Rat and mouse	Infliximab can inhibit choroidal neovascularization secondary to glaucoma	[50, 51]

CONTRIBUTION OF TNF-α TO AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) affects the aging human population worldwide and may lead to irreversible sight loss [63]. Because of its strategic location and vital roles, the retinal pigment epithelium (RPE) is the primary site associated with AMD [64]. RPE is a single layer of pigmented epithelial cells with a highly organized structure and tight junctions. It acts as a barrier

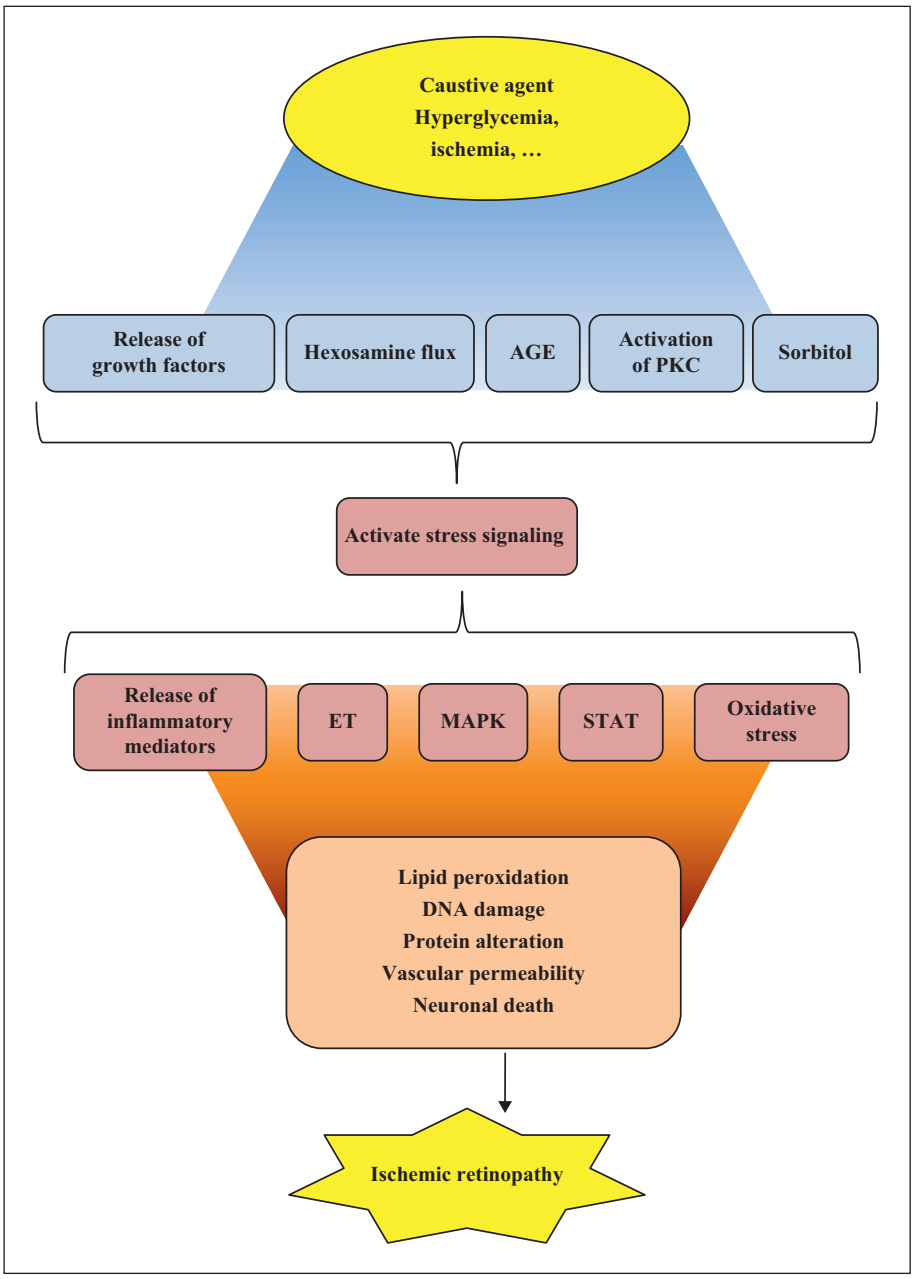

Figure 3
Major axes in the ischemic retinopathy pathogenic cascade. AGE: advanced glycation end-products; PK: protein kinase C; MAPK: mitogen-activated protein; ET: endothelins; STAT: signal transducer and activators of transcription.

Table 3
Summary of reports that examined the use of TNF-α antagonists in the treatment of ischemic retinopathy:

TNF-α inhibitor	Species	Effect	References
Etanercept	Rat	Blocking TNF-α activity plays an important role in the treatment of ischemic retinal diseases	[62]

between the neuroretina and the highly vascularized choroid on the posterior side [65]. Taking into account clinical and pathological features, two subgroups of AMD are classically distinguished: atrophic (dry form) and exudative (wet form). The dry form is typically characterized by a progressing course leading to degeneration of RPE and photoreceptors. The exudative form is linked to choroidal neovascularization directed to the subretinal macular region, with subsequent bleeding and/or fluid leakage, which may result in a sudden loss of central vision; it is the most rapidly progressing form of AMD [66]. The major axes in the pathogenic cascade of AMD are summarized in *figure 4*.

Clinico-pathological, epidemiological and gene mapping studies indicate a strong association of inflammatory processes in the initiation and/or progression of AMD [67]. Accordingly, overexpression of the pleiotropic TNF-α has been found in neovascular membranes of eyes with AMD [68]. Several lines of evidence suggest that interactions between TNF-α and its receptor(s) are important for the regulation of RPE cell activities, including cell attachment, spreading, chemotaxis, migration and proliferation [69]. Moreover, expression of various apoptotic factors in RPE cells in AMD is up-regulated by TNF-α [70]. In addition, Nagineti *et al.* demonstrated that TNF-α increases the secretion of vascular endothelial growth factor (VEGF) A and C by human RPE cells and choroidal fibroblasts, with VEGF being the most important factor for initiating pathological ocular neovascularization [71].

Neutralization of TNF-α activity in the clinical setting results in deactivation of the proinflammatory cytokine cascade, diminished recruitment of inflammatory cells from blood to the site of inflammation, decreased angiogenesis mediated by VEGF, and alterations in chemokines and

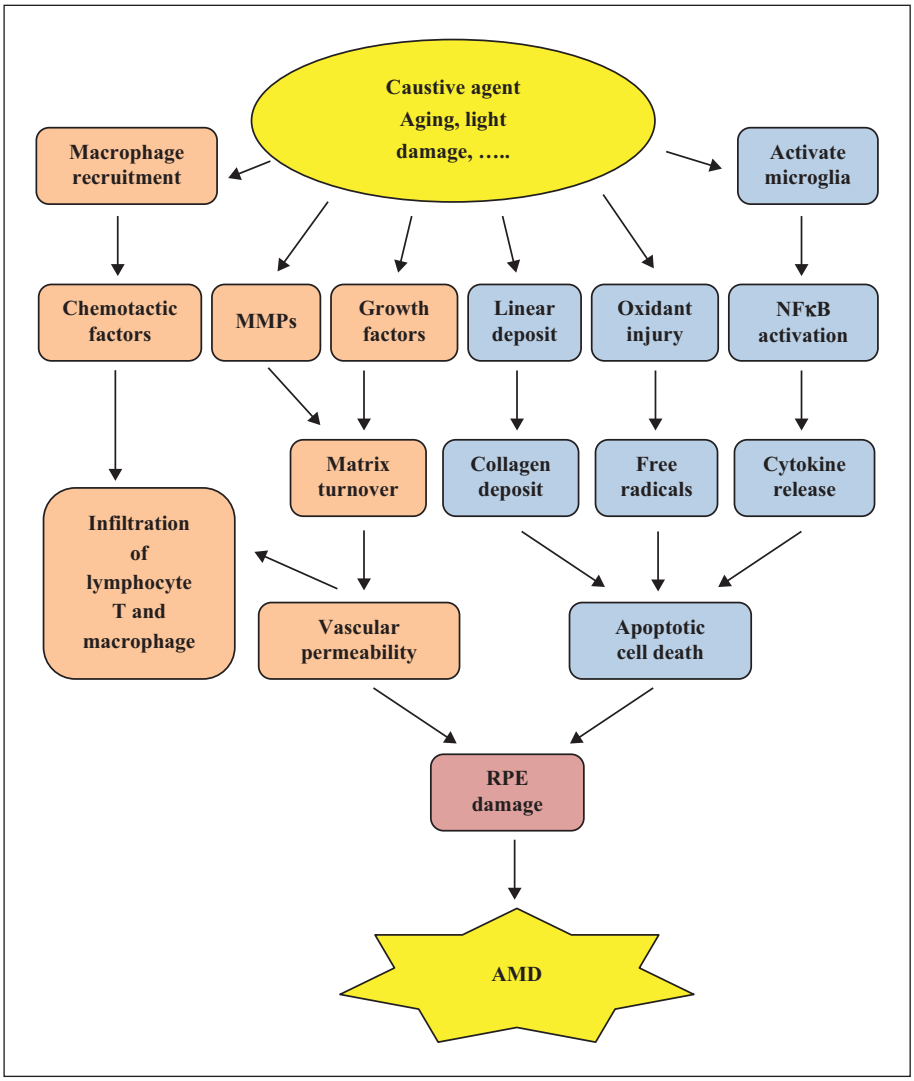

Figure 4
Major axes in the ischemic age-related macular degeneration cascade. AMD: age-related macular degeneration; MMPs: matrix metalloproteinase; NFκB: nuclear factor kappa B; RPE: retinal pigment epithelium.

Table 4
Summary of reports that examined the use of TNF-α antagonists in treatment of AMD:

TNF-α inhibitor	Species	Effect	References
Infliximab	Human	Plausible pathogenic role of TNF-α in AMD	[68]
		Inhibition of TNF-α actions with the monoclonal antibody infliximab may be of benefit to AMD patients	[73]
	Rat, mouse	Intravitreous infliximab injection reduced angiogenesis, whereas opposite effects were observed at high doses	[74]
Adalimumab	Monkey	Therapeutic value of Adalimumab in the treatment of AMD	[75]
Etanercept	Human	Etanercept significantly reduced the development of choroidal neovascularization lesions	[51]

vascular permeability [72]. Therefore, a drug that interferes with TNF/TNF-receptor interactions may represent a legitimate therapeutic approach for patients with neovascular AMD. Since their introduction, ophthalmologists have used TNF-α blockers to treat several ocular diseases (*table 4*).

CONTRIBUTION OF TNF-α TO RETINITIS PIGMENTOSA

Retinitis pigmentosa (RP) is defined as a heterogeneous group of inherited retinal disorders that are characterized by pigment deposits predominantly in the peripheral retina and a relative sparing of the central retina. In most cases of RP, there is a primary degeneration of the photoreceptor rods, with secondary degeneration of cones. Thus, typical RP is also described as a rod-cone dystrophy, photoreceptor rods being more affected than cones. This sequence of photoreceptor involvement explains why patients initially present with night blindness with peripheral visual field loss, and only in later life suffer from visual impairment in diurnal conditions [76, 77]. It is the most common of the retinal degeneration conditions with a prevalence of approximately 1 in 3,000 to 1 in 5,000, affecting approximately 1.5 million people worldwide [78].

The molecular mechanisms by which gene mutations lead to photoreceptor apoptosis have not been clearly elucidated. It is thought that retinal inflammation does not play a prominent role in the pathophysiology of the disease [79]. In contrast, some studies have revealed that several inflammatory events, accompanied by microglia activation, are involved in photoreceptor degeneration [80, 81]. A study on rd mice, a widely used retinitis pigmentosa animal model, showed that the activation of microglia, as well as expression of chemokines and microglia-derived TNF-α, coincided with or preceded the occurrence of gene mutation and photoreceptor apoptosis, suggesting that an inflammatory response may play an important role in the retinal degeneration in rd mice [81]. Furthermore, Zeng and coworkers reported an increase in TNF-α production by microglia cells in the retinal degeneration in rd mice [82]. They suggested that TNF-α may serve as both target and inducer gene of NFκB in RP. Recently, TNF-α gene expression was found to be upregulated in two models of retinal degeneration that are characterized by rhodopsin abnormalities, suggesting the TNF-α pathway as major cell death pathway in RP [83].

Changes in TNF-α and NFκB levels may promote photoreceptor apoptosis via initiation and perpetuation of chronic inflammation in the rd retina, making this pathway an extremely attractive target for therapeutic intervention. Further studies are required to investigate the exact role of TNF-α and its signaling pathways in photoreceptor degeneration and the possible therapeutic use of TNF-α antibodies in the treatment of RP.

CONCLUSION

TNF-α is a pleiotropic cytokine that is involved in a wide range of physiological functions. Increased expression of TNF-α causes apoptosis of various retinal neurons such as RGC, leading to retinal neurodegenerative disorders. The usefulness of the concept of neuroprotection relies heavily on the understanding of the pathophysiological mechanisms involved in the onset and progression of neurodegenerative disorders. TNF-α has been shown to have direct as well as indirect toxicity towards a variety of retinal neurons and photoreceptors by acting as an upstream regulator. Therefore, TNF-α is an attractive target for the treatment of neurodegenerative disorders: anti-TNF-α therapy has been shown to be effective in several neurodegenerative diseases that involve TNF-α as a key mediator. Efforts should also be made to target downstream mechanisms of the TNF-α signaling pathway.

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