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REVIEW

Transcription Factor NF-κβ and Molecules Derived from its Activation in Age-Related Macular Degeneration

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ABSTRACT
Activation of the nuclear factor kappa β (NF-κβ) is related to many inflammatory diseases, including age-related macular degeneration (AMD). The imbalance in the redox state, which happens mainly in senescence, associated with several peculiar characteristics of the macular region, has led to studies of this molecule for AMD therapeutic interventions. Findings report the involvement of NF-κβ both in the triggering as well as in the worsening condition of AMD. The present article correlates AMD oxidant and inflammatory genesis with the action of the nuclear factor kappa β. Besides its mechanism of action, this study also analyzes the main inflammatory cytokines and adhesion molecules that may be activated by NF-κβ and are closely related to AMD

KEYWORDS: Macular Degeneration; NF-κβ; Oxidation; Inflammation; Cytokines

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INTRODUCTION

Age-related macular degeneration is the main cause of irreversible loss of vision in the elderly in developed countries (1,2). Although AMD physiopathogenic mechanisms are not completely explained, some peculiarities of the macular region that induce its degeneration have already been established. The retina is a tissue exposed to oxidative stress due to its high metabolism, large concentrations of polyunsaturated fatty acid content, exposure to visible light (between 400 - 700 nm) and the presence of photosensitive molecules such as rhodopsin and lipofuscin (3). The oxidative and nitrosative stress to which the retina is exposed is induced by the imbalance between the antioxidant defense and the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and plays an important role in the triggering and progression of AMD (3-5). Photosensitive reactions, for example, generate ROS and RNS, such as superoxide ($O2^{-}$ •), hydrogen peroxide (H2O2), singlet oxygen (1O2), and peroxynitrite (ONOO-), which induce damage to retinal pigment epithelial (RPE) cells (6,7). The hypofunctioning RPE cells inhibit the appropriate degradation of the products resulting from the phagocytosis of the photoreceptor outer segment cells, causing the pathological accumulation of lipids in the Bruch's membrane (8,9), producing druses and other extracellular deposits in the Bruch's membrane. These deposits are considered important risk factors for the development of AMD (8,9). The druses, as well as the choriocapillaris, the photoreceptors and the RPE cells, present inflammatory and immunological markers (10-22). Additionally, microglia, the immune cells responsible for the coordination of responses to inflammatory stimuli of the retina (23-24), as well as the RPE cells and the macrophages, secrete cytokines, enzymes, and growth factors, responsible for the triggering and the progression of AMD (25-28).

Inflammation is an important activator of the nuclear factor kappa β (NF-κβ). When activated, this transcription factor induces an increase in inflammatory cells and molecules perpetuating the cycle (29). Additionally, NF-κβ is also a redox-sensitive transcription factor, that is, its activation is triggered by the cell oxidative stress (30-35). Several studies correlate NF-κβ with AMD (36-39). Hence, this review discusses the role of the nuclear factor kappa β (NF-κβ) and its activated inflammatory molecules in AMD genesis.

NF-kβ

Transcription factors are proteins responsible for the coordinated expression of genes through specific binding to gene promoter and enhancer sites (40). NF-κβ transcription factor was discovered in 1986. It was first identified in T lymphocytes, and later observed in all mammal cells (41-42). It plays an important role in the cell survival and proliferation, as well as in its apoptosis (43-44). Additionally, it helps to regulate the expression of genes associated with the immune and inflammatory responses (45-46). It is important to note that this transcription factor mediates the synthesis of cytokines such as tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), Interleukin-2 (IL-2), Interleukin-6 (IL-6), and Interleukin-8 (IL-8), as well as the expression of the cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), and acute phase proteins, such as c-reactive protein (CRP). Besides the response it provides to the acute inflammation, NF-κβ is a master regulator of the chronic inflammatory processes (47-48). Such cytokines may cause oxidative stress-induced cell dysfunction or cell death (49). NF-κβ activation is also related to the increase in the expression of the adhesion E-selectin, intercellular adhesion molecule-1 (VCAM-1), and vascular cell adhesion molecule-1 (ICAM-1), whereas inhibition of NF-κβ decreases the transmigration and the leukocyte adhesion (50).

NF-κβ family (or Rel family) is composed of five subunits: p65 (RelA), c- Rel, RelB, p50 and p52. It is characterized by including a well-preserved N–terminal domain with around 300 amino acids (RHD – *Rel homology domain*), which subdivides into two domains, the DNA-binding and the dimerization one (43, 51-53). NF-κβ subunits homo- or hetero-dimerize to form activating dimers (p50-p65) or repressors (p50-p50 e p52-p52). They are found in the cytoplasm of most cells in an inactivate state, binding with the inhibitory proteins of the inhibitory kappa B (IκB) family, among which the most important are IκBα, IκBβ, and IκBε. IκBα is associated with the transient activation of NF-κβ, whereas IκBβ is involved in sustaining the activation (54-57).

There are two pathways to activate the NF-κβ: the classical (canonical) and the alternative (non-canonical) pathways. The classical one is more common and is associated with inflammation-related genes, innate immunological response, anti-apoptosis and cell survival (40). Conversely, the alternative pathway is associated with the expressions of genes that contribute to develop and maintain the secondary lymphoid organs (58). When not activated, NF-κβ factor is found in the cytoplasm, binding to an inhibitory protein, IkB. This complex prevents the translocation of NF-κβ into the nucleus. Hence, IkB phosphorylation and degradation are required for translocation to occur (43-44,54,59). After IκB degradation, NF-κβ dimers (E.g. p50-p65) are released and migrate into the nucleus where they will bind with κB target gene enhancers, inducing the transcription of genes that mediate several cellular processes such as immunity, inflammation, proliferation, apoptosis and cellular senescence (60-62).

Several internal and external cell stimuli may contribute to this activation, such as neurotrophins, neurotoxic proteins (such as β-amyloid), cytokines (Interleukin-1 and TNF-α), glucocorticoid, phorbol esters, atrial natriuretic peptide, ceramides, virus- and bacteria-derived products, ultraviolet irradiation, ionizing radiation, enzyme reaction products such as iNOS and COX-2 (29,47,63-66). It is important to point out that during chronic inflammation, several immunological cells are continuously activated by inflammatory mediators, and when inflammation is not resolved, the cells recruited by the inflammatory mediators secrete additional mediators, inducing a vicious cycle that activates NF-κβ in a chronic way (29).

THE ROLE OF NF-κβ IN AMD PATHOGENESIS

It is possible to infer that, due to the fact that NF-κβ is activated by the oxidative stress and the inflammatory cytokines, such as TNF-α and IL-1β, as well as by the concentration of UV rays, the macular region meets the appropriate conditions for its activation (63-64,67-68). Besides these factors, the chronic oxidative stress induces the production of advanced glycation end products (AGE) and their receptors (RAGE). It is important to point out that increased RAGE or AGE levels were identified in RPE cells for isolated samples of AMD patients (69-70). It is known that the increase in AGE and RAGE activates NF-κβ in RPE cells (70).

Activation of NF-κβ induces an increase in the expression of several inflammatory cytokines and adhesion molecules that can potentially trigger and/or worsen AMD. Among those to be highlighted are:

Tumor necrosis factor-α (TNF-α)

TNF-α is a low molecular weight protein, produced, predominantly, by activated macrophages. It has the potential to modulate the production and expression of the vascular endothelial growth factor (VEGF) receptors (71-72). This cytokine may play a cell protective or destructive role. These characteristics may be closely associated with its receptors tumor necrosis factor receptor superfamily member 1A (Tnfrsf1a) and tumor necrosis factor receptor superfamily member 1B (Tnfrsf1b). It is known that activation of Tnfrsf1a induces inflammation, inhibition of the endothelial cellular migration and apoptosis of the endothelial cells (73). Additionally, it has shown potential to inhibit the choroidal neovascularization (CNV). Conversely, Tnfrsf1b receptors regulate lymphocyte proliferation (74) and promote endothelial cell activation, migration, and survival (75-76). In this regard, Tnfrsf1b, unlike Tnfrsf1a, may promote CNV (77). An experimental study reported that TNF-α down-regulates VEGF secretion in polarized RPE cells but up-regulates it in non-polarized RPE cells. These results are due to the opposing activity levels of the c-Jun N-terminal kinase (JNK) and NF-κβ pathways. In certain clinical conditions, such as AMD, the RPE cell polarity changes at different stages of the disease with the RPE cells being polarized early on, and some RPE cells losing their cellular polarity at the later stages (36). In the physiopathogenesis of the choroidal neovascular membrane (CNVM), experimental and clinical studies demonstrated that intervention in this cytokine may improve angiogenesis progression (78-80). TNF-α also stimulates the production of Interleukin-6 (81).

Interleukin-6 (IL-6)

IL-6 is a multifunctional cytokine that acts upon a wide range of cell tissues and linings. It is considered a potent mediator of the inflammation and immune response (81-

82) and is a marker for systemic inflammation. Human RPE cells constitutively express and release IL-6 at a relatively low level (83). Several AMD studies have reported IL-6 to be an important regulator of CNV, as it also acts upon VEGF expression (47,84-87). Increase in IL-6 levels were observed in a laser-induced CNV mouse model and the blockage of its receptors induced a significant decrease in the expression of monocyte chemoattractant protein-1 (MCP-1/CCL2), VEGF and inhibited macrophage infiltration into the CNV areas (88). A prospective cohort study demonstrated that elevated IL-6 may serve as marker for the progression of AMD (89). However, another study found no significant association between plasma IL-6 levels and AMD, or AMD progression (90). The inhibition of NF-κB activation decreased the H2O2-induced increase of IL-6 release by RPE cells, demonstrating NF-κB effect on this inflammatory interleukin (91).

Inducible Nitric Oxide Synthase (NOS-2 or iNOS)

Nitric oxide synthase (NOS) is a family of enzymes that catalyzes the production of nitric oxide (NO), from L-arginine. This family presents three isoforms: NOS-1 or neuronal (nNOS); NOS-2, or inducible or immunological (iNOS); and NOS-3 or endothelial (eNOS). The three isoforms are found in different eye tissues (92,93). Overproduction of the free radical NO has been associated with the pathogenesis of a variety of inflammatory and immunologically mediated diseases as well as with the induction and progression of AMD (94). Activation of NF-kβ induces not only the iNOS expression, but also the pathological conditions caused by the endotoxins or the cytokines such as IL-1, IL-6, and TNF-α. Upon induction, iNOS will produce a large amount of NO for a long period of time (95). In this condition, NO is converted into NO2, nitrite, peroxynitrite and free radicals to induce pathophysiological alterations such as AMD (94-96). It has been demonstrated that a specific NF-kB inhibitor, pyrrolidine dithiocarbonate (PDTC), reduced iNOS expression in RPE cells treated with linoleic acid (LA) (37).

Interleukin-1β (IL-1β)

IL-1β is a pro-inflammatory cytokine that may initiate innate immunological processes associated with inflammation, infection, and immunity (97-98). In the retina, immunoreactivity to IL-1 has been observed in the astrocytes and Müller cells (99). IL-1β is secreted as an inactive form and requires proteolytic cleavage by the caspase-1 enzyme to be released in an active form (100). Caspase-1 activation platform, known as inflammasome, has been associated with AMD physiopathogenesis (101-102).

A study on AMD experimental models, with geographic atrophy of the choroid, has reported that mononuclear phagocytes express IL-1β, responsible for the lesion of cone outer elements and death of rods (103-105). Another study demonstrated that IL-1β induces rod degeneration through the disruption of retinal glutamate homeostasis (106). Additionally, patients with polypoidal choroidal vasculopathy and wet AMD presented a significant increase in the expression of IL-1β in vitreous (107). Suppression of IL-1β expression by salicin has shown to inhibit activation of NF-kβ in retinal endothelial cells, representing a potential therapeutic approach to treat CNV in AMD (108).

Interleukin-2 (IL-2)

IL-2 plays crucial roles in regulating both immune activation and homeostasis (109). It is mainly produced by activated T cells, especially CD4+, and is synthesized in smaller amount by B cells and monocytes. IL-2 is one of the main T-cell stimulating factor (110) and has already been associated with AMD (111). A study has reported an increased activation of the inflammation pathway IL-2, which is consistent with the conclusions drawn from clustering analysis of several AMD phenotype-specific RPE-choroid modules that inflammation is a prevalent functional category (112). Another study investigated the effects of IL-2 on epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) synthesis and transforming growth factor β2 (TGF-β2) expression in RPE cells. The results indicated that the signal transducer and activator of transcription 3 (STAT3) and NF-κβ signaling pathways might interact with each other and play important roles in IL-2-induced fibrosis in RPE cells together. These findings can offer new insights about the molecular mechanisms underlying the pathogenesis of AMD (113).

Interleukin-8 (lL-8)

IL-8 was identified in 1987 as a novel type of neutrophil-activating cytokine. It is released by phagocytes and a wide variety of tissue cells upon exposure to inflammatory stimuli (114). IL-8 also promotes an increase in the expression of adhesion molecules by the endothelial cells and activates the polymorphonuclear neutrophils, increasing the oxidative metabolism (115).

A meta-analysis suggested that IL-8 +781 C/T polymorphism affects predisposition to AMD and wet AMD. Moreover, patients with AMD and wet AMD also present elevated IL-8 levels (116). A case-control study suggested a possible secondary role of IL-8 gene in the development of AMD and regarded IL-8 as a new susceptibility genomic biomarker of AMD (117). The intraocular IL-8 concentrations have been elevated in patients with exudative AMD (118) and correlated with the size of an active CNV (119). Studies have shown that NF-kβ activity is upregulated in the presence of 25-hydroxycholesterol (25-OH), a potent inducer of IL-8 expression and secretion in human adult retinal pigment epithelial (ARPE-19), and that this transcription factor is, at least, partially involved in IL-8 production upon 5-OH treatment (120).

Cyclooxygenase 2 (COX-2)

COX-2 belongs to an enzyme group formed by COX isoforms COX-1, COX-2 and COX-3, which is involved in inflammatory immune responses required for the conversion of arachidonic acid to prostaglandins (121). It mediates inflammation and is induced by pathological stimuli including cytokines, growth factors, inflammatory mediators, and bacterial lipopolysaccharides (121-122). In humans, COX-2 is detected in the outer plexiform layer and in RPE cells (123,124). COX-2 has been shown to modulate the expression of VEGF ligand and its receptors, an important mediator in the development of ocular neovascularization (125). COX-2 involvement has been associated with CNVMs and subretinal fibrosis of the

retina (125). It has been shown that COX-2 could stimulate macrophages to produce TGF-β, which consequently synthesizes and deposits collagen fibers, eventually leading to fibrosis (126). An experimental study on wet AMD demonstrated that COX-2-selective inhibitor reduces subretinal fibrosis in vivo and in vitro (127). This experiment confirmed the role of COX-2 in the AMD physiopathogenesis. Corroborating the experimental findings, the immunohistochemical analysis of CNVs in humans revealed an expression of COX-2 in 69% of the cases, confirming the theory that inflammation is an important component in the development and progression of neovascular AMD in some patients (128). Research has shown that a specific NF-kB inhibitor, the pyrrolidine dithiocarbonate (PDTC), significantly reduced the expression of COX-2 in RPE cells treated with the LA, a fatty acid involved in AMD genesis, indicating that activation of NF-kB was involved in LA-induced expression of COX-2 (37).

C-reactive protein (CRP)

CRP is a highly conserved acute phase protein of the pentraxin family that consists of 5 noncovalently linked subunits of ≈23 kDa. It is predominantly produced in the liver, although, under certain conditions, it can also be secreted by smooth muscle cells and endothelial cells (129,130).

CRP is released into circulation upon stimulation by IL-6 and other cytokines (131). Several studies suggest a close association between serum CRP and AMD (132-134).

A meta-analysis study showed that high serum levels (> 3 mg/L) of CRP are associated with a two-fold likelihood of late onset AMD, compared to low levels (< 1 mg/L) (135). The Rotterdam study found that elevated baseline levels of highly sensitive CRP were associated with the development of early and late AMD in the large population-based cohort (136).

A study on genotyped human donor eyes reported that eyes homozygous for the high-risk CFH (Y402H) allele had elevated monomeric CRP (mCRP) within the choriocapillaris and Bruch's membrane, compared to those with the low-risk genotype. This study indicated that mCRP is the most abundant form of CRP in human choroid, and that mCRP levels are elevated in individuals with the high-risk CFH genotype. Moreover, pro-inflammatory mCRP significantly affected endothelial cell phenotypes in vitro and ex vivo, suggesting a substantial role for mCRP in choroidal vascular dysfunction in AMD (137). Significant CRP deposition has shown to trigger and exacerbate the inflammatory response in RPE cells promoted by the induction of pro- inflammatory cytokines such as IL-8. This induction is mediated by NF-kB and multiple Mitogen-activated protein kinase (MAPK) pathways through Fc gamma receptors. Thus, it might contribute to the accumulation of immune cells observed in areas of drusen formation and choroidal neovascularization (138).

E-Selectin

E-selectin, known as the endothelial leukocyte adhesion molecule 1 (ELAM-1), is responsible for the regulation of the first processes in the adhesion cascade, binding and rolling of leukocytes into the endothelium. E-selectin is inducibly expressed in endothelial cells (139).

An immunohistochemistry study demonstrated that subfoveal CNVMs surgically excised from AMD patients presented higher ICAM-1 and E-selectin immunostaining when compared with those in the normal eye and that the increase in ICAM-1 and E-selectin immunoreactivity occurs primarily in the periphery of the CNVMs, where there are larger numbers of vessels. However, this immunoreactivity was not identified on any larger patent vessels in the central, fibrotic regions of the CNVMs (140). An experimental wet AMD study reported an increase in E-selectin in RPE, in the choroidal vascular endothelial and inflammatory cells (141). However, another study was not able to demonstrate an association between the E-selectin single nucleotide polymorphism (SNPs) and AMD development (142).

Intercellular Adhesion Molecule 1 (ICAM-1)

ICAM-1 or CD-54 is a glycoprotein of the immunoglobulin superfamily. Like other adhesion molecules, ICAM-1 is distributed in the endothelial cells and leukocytes, participating in the leukocyte recruitment to damaged or inflamed tissue (143). It is known that, in the normal eye, ICAM-1 is expressed in low levels in the choroid and retina vascular endothelium, as well as in the RPE, Bruch's membrane and outer limiting membrane (144-146). It was also demonstrated that ICAM-1 presents a higher concentration in the macular region than in the peripheral region (147). This finding suggests a higher susceptibility of the macula for the traffic of immune cells, including the macrophages, which accounts for the higher incidence of CNV in this region. It is known that the macrophages, besides producing VEGF (26), are also sources of inflammatory and proangiogenic cytokines, which mediate the inflammatory response and contribute, significantly, to the formation of CNVM (89,148-151). In a hypercholesterolaemic experimental model, an increase in the ICAM-1 and interleukin-6 expression in the sclerochoroidal complex was observed (152). In pathological conditions, as well as in AMD, a significant increase in the expression of ICAM-1 in RPE vessels and cells was observed. This increase in immunoreactivity was primarily observed in CNVM periphery, where there are a large number of vessels (153). Other experiments have also reported an increase in the ICAM-1 expression in the RPE, choroidal vascular endothelial and inflammatory cells in wet AMD (144, 154).

A study on CD18-and ICAM-1–deficient mice reported that they developed less CNVM when compared with normal mice, suggesting that this immunoglobulin plays an important role in the formation of CNVM (155). The analysis of the aqueous humor of patients who underwent cataract surgery revealed that concentrations of MCP-1, soluble intercellular cell adhesion molecule-1 (sICAM-1), and soluble intercellular cell adhesion molecule-1 (sVCAM-1) were significantly associated with exudative AMD, even in the presence of normal VEGF concentrations. This study concluded that MCP-1, sICAM-1, and sVCAM-1 could potentially be additional target molecules in the treatment of exudative AMD (156).

It has been demonstrated that the expression of ICAM-1 and MMP-9 in ARPE-19 cells may be reduced by quercetin, a flavonoid polyphenolic, via the MEK1/2-ERK1/2 and PKCδ-JNK1/2-c-Jun or NF-κB pathways (157). Another study corroborates this finding by demonstrating that an NF-κB inhibitor (Bay 11-7082)

reduced the expression of ICAM-1, sICAM-1, IL-6, IL-8 and MCP-1 in ARPE-19 cells (158).

VCAM-1 (Vascular cell adhesion protein 1)

VCAM-1 is expressed in endothelial cells in response to cytokines (e.g., TNFα and IL-1β) and mediates adhesion of leukocytes including lymphocytes and monocytes (159-160). VCAM-1 is over-expressed in a number of human ocular diseases (161-162).

An experimental study aiming at assessing the role of inflammation as a mechanism of vision loss and degeneration of the sensory retina underlying CNV, reported extensive macrophage recruitment in the retina under CNV. Macrophages were closely associated with retinal blood vessels strongly immunoreactive for VCAM 1, ICAM 1, or platelet-endothelial cell adhesion molecule (PECAM). The macrophage infiltration was responsible for the Müller cell activation, suggesting that macrophages induce degenerative changes in the retina under CNV (163).

A longitudinal population-based cohort study examined the relationship between serum markers of inflammation, oxidative stress, and endothelial dysfunction with a 20-year cumulative incidence of early AMD. It reported a modest relationship of serum high-sensitivity CRP, TNF-α receptor 2, and IL-6 to soluble VCAM-1 of early AMD, regardless of age, smoking status, and other factors (164).

CONCLUSION

Activation of NF-κβ induces an increase in the expression of genes associated with inflammatory cytokines, enzymes, and adhesion molecules, which, in turn, are closely related to AMD. The molecules derived from the activation of this nuclear transcription factor, such as TNF-α, IL-6, IL-8, COX-2, and ICAM-1, have been considered therapeutical targets of experiments related to macular degenerative disease. The other molecules, despite having their role in AMD physiopathogenesis determined, have not, surprisingly, received the same attention. Currently, AMD treatment is predominantly provided with anti-VEGF substances. By analyzing the large number of molecules involved in AMD genesis, mainly those derived from NF-κβ activation, we may expect that more preventive and therapeutic treatments will be offered in the next decades.

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COMPETING INTERESTS

The authors declare no competing interests with this case.

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