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Diana Florina Tricorache
Carol Davila University of Medicine and Pharmacy, Doctoral School, Bucharest, Romania

Ana Maria Dascalu
Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania

Crenguta Serboiu
Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania

Anca Bobirca
Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania

Dragos Cretoiu
Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania

See next page for additional authors

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The role of inflammation in age-related macular degeneration

Diana Florina Tricorache[1#], Ana Maria Dascalu[1,2*], Crenguta Serboiu[2#], Anca Bobirca[2], Dragos Cretoiu[2], Dan Bratu[3#], Corneliu Tudor[2], Laura Carina Tribus[4]

[1] *Carol Davila University of Medicine and Pharmacy, Doctoral School, Bucharest, Romania*
[2] *Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania*
[3] *Lucian Blaga University of Sibiu, Faculty of Medicine, Bucharest, Romania*
[4] *Carol Davila University of Medicine and Pharmacy, Faculty of Dental Medicine, Bucharest, Romania*

 # All authors contributed equally to this work and thus share first authorship

ABSTRACT

Age-related macular degeneration (AMD) is a complex, chronic, and progressive disease which affects the macular area, being one of the leading causes of irreversible vision loss worldwide. Specific alterations of retinal structure occur at the macular level, which regarding its severity can range from the presence of drusen to the development of geographic atrophy or choroidal neovascularization. AMD has long been considered a degenerative disease, but new studies highlight the role of inflammation present both in the atrophic form and in the exudative form. The present review is based on comprehensive research on PubMed and Web of Science databases, and it aims to describe the inflammatory pathways involved in AMD onset and progression. Understanding the molecules involved in AMD pathogenesis, and their mechanism of action, is crucial because they can be both biomarkers with a predictive role in disease management, as well as potential therapeutic targets.

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***Corresponding author:**
Ana Maria Dascalu,
Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Doctoral School, Bucharest, Romania
E-mail: ana.dascalu@umfcd.ro

Introduction

AMD is the leading cause of blindness in industrialized countries [1,2], and one of the most frequent causes of visual impairment and blindness worldwide, ranking the third place after cataract and uncorrected refractive errors [3]. Moreover, while cataract and refractive errors are curable, and national and international programs, such as Vision 2020 aim to diminish the cases of preventable blindness [4], there is still little progress in understanding and treating options for AMD, which remain a major burden on national healthcare systems. It is estimated that approximately 200 million people worldwide suffer from this disease currently, and the prevalence is on an increasing trend due to population aging [5-7]. During Covid-19 pandemic, several studies reported disruptions in providing ophthalmic care in AMD patients, with possible long-term effects upon visual function [8-10].

Central vision loss is the main clinical feature in AMD and it occurs as a result of the degenerative process of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris, although the earliest manifestation seems to be a histopathological anomaly occurring in Bruch's membrane [5,11]. Drusen is a subretinal accumulation, located between retinal pigment epithelium (RPE) and Bruch's membrane [5,6,11]. According to the AREDS (Age-Related Eye Disease Studies) group, it is subdivided into 4 categories depending on the size of the drusen and other changes present at the retinal level: the presence of hard drusen, without other changes; Early AMD, with bigger sized drusen (63-125 microns), without other changes at the RPE level; Intermediate AMD, with drusen larger than 125 microns and associated pigmentary changes of RPE; Advanced AMD. There are 2 subtypes of advanced AMD: the dry form (atrophic AMD) represented by chorioretinal atrophy assuming a geographic pattern, and the wet form (exudative AMD) represented by the development of a choroidal neovascular membrane [12]. A recent study of Fleckenstein et al. estimates that people aged 75 and older have a 25% risk of early AMD and a risk of 8% for advanced AMD [2]. While significant improvements in wet AMD therapy were brought by anti-

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VEGF agents, currently there is no effective treatment for the atrophic form.

Age-related macular degeneration is a consequence of a multifactorial interaction involving environmental factors, metabolic factors, and genetic factors, all of which lead to structural changes at the macular level [13]. Risk factors have been extensively studied, the most important being age, alterations in lipid metabolism, antioxidant deficiencies, and genetic predisposition, out of which new therapeutic possibilities emerged such as antioxidant supplementation [2,11]. Recent evidences point out the important role of inflammation in the disease activity, which may be relevant for developing future therapies.

The present review is based on a comprehensive search on Web of Science, PubMed and Google Scholar databases, between 2000 and 2023, based on all previously published articles regarding the role of systemic and local inflammation in the onset and progression of AMD.

Discussions

Inflammation and pathogenetic mechanisms in AMD

Both systemic and local inflammation were correlated with progression of AMD lesions. Serum elevated cytokines, such as Il-6, Il-12, TNF alfa was correlated with higher VEGF values in patients with AMD and adverse outcomes after anti-VEGF therapy in patients with wet-AMD [14,15]. Cytokines and pro-inflammatory molecules aggravate retinal damages and photoreceptors degeneration [16-18]. Moreover, IL-6 induces endothelial cell dysregulation, leading to vascular leakage, coagulation and local ischemia [19,20].

The retinal pigment epithelium, a single-cell layer, with numerous functions including maintenance of photoreceptor cell layer functionality, protecting the retina from light damage, forming a blood-retinal barrier, and perhaps most importantly, especially for the pathogenesis of AMD, involvement in the immune response at the macula, is responsible for the secretion of immunomodulatory factors that mediate immune-type inflammation [21,22].

A study conducted by Hageman and colleagues demonstrated that the presence of drusen is associated with the presence of an inflammatory response, this association being attributed to the multiple components found in it [23]. Among these, the most important are classic markers of the acute phase and components of the complement cascade [23,24]. Also, the retinal pigment epithelium (RPE) and dendritic cells play an important role in the appearance of drusen and the inflammatory response [25].

RPE is extremely sensitive to excessive oxidative stress [26]. This is due, on one hand, to its increased metabolic activity, associated with increased oxygen consumption, and on the other hand to the high content of polyunsaturated fatty acids [11,26]. A major function of RPE is represented by autophagy which degrades the external segments of photoreceptors, a process called heterophagy. This continuous ingestion, especially by an RPE in the physiological aging process, leads to the accumulation of lipofuscin (a non-degradable and autofluorescent metabolite) in lysosomes [26,27]. Lipofuscin will inhibit autophagy by blocking lysosomal functions, thus combining the effect of oxidative stress with inflammation, acting as a trigger for an immune response [25,27].

Immune response activation in AMD

It starts with the activation of inflammasomes, some small factories of cytosolic molecules composed of a sensor protein -PRR (pathogen recognition receptor), an adapter protein associated with apoptosis that contains a caspase recruitment domain, and a proinflammatory caspase [13]. In most studies so far, NLPR3 (from the PRR family) is the receptor responsible for inflammasome activation at the RPE level, being stimulated by a variety of molecules including lipofuscin and drusen component molecules [28]. PRR activation leads to the secretion of chemokines and cytokines - IL-1β, IL-12 IL-16, TNF-α, and IL-8 to which cells will answer [13,24].

IL-1β and TNF-α effects include endothelial cell activation, which increases their expression of leukocyte adhesion molecules, cytokines, growth factors, and HLA molecules [29]. They will also change their phenotype, becoming prothrombotic in an attempt to limit the spread of the pathogen. The prothrombotic status leads to an increase in vascular permeability, thus circulating leukocytes will adhere to adhesion molecules. Once they reach the site of inflammation, the leukocytes extravasate to the tissue level, being accompanied by other plasma proteins [13,30].

IL-8 is responsible for attracting neutrophils, being the first cells dispatched at the site of inflammation, where their activation will occur [31]. Once activated, neutrophils destroy pathogens through several mechanisms: 1. reactive oxygen species production; 2. through the release of active peptides, and 3. through the formation of neutrophilic extracellular fibers (NET) that release protein granules and chromatin [24]. NET can promote adaptive immunity even in sterile inflammation conditions. Also, neutrophils are involved in angiogenesis through the production of VEGF [32].

Monocytes are the next type of cells that reach the inflammatory focus, where, depending on the local conditions, they will differentiate into dendritic cells and macrophages. Both macrophages and dendritic cells are effective cells when it comes to antigen presentation (APC-antigen presenting cells), they can internalize the antigen to present it later to other inflammatory cells: T-effector cells [13,33].

Macrophages are very flexible in terms of phenotype, being able to change their phenotype depending on the environment they are in [34]. M1-type macrophages are activated by IFN-γ and TNF-α, in turn producing numerous cytokines with pro-inflammatory roles such as IL-6, IL-12, TNF-α, and nitric oxide, all leading to the Th1-type immune response [34,35].

M2 macrophages are activated by IL-4 and IL-13 which act as direct activators, being TH2-type cytokines. M2 macrophages have an important role in tissue regeneration, maintaining homeostasis, maintaining inflammation, hypersensitivity, and the appearance of choroidal neovascularization [13,36].

Inflammation and atrophic AMD

So far, inflammation and its role in AMD has been investigated more and more. However, we cannot deny the role that inflammation has in the atrophic form [37]. Drusen, the characteristic lesion appears as a result of the accelerated progression of the signs of aging, being an accumulation of lipofuscin and other toxic elements - melanin granules, lipids, lipoproteins, apolipoprotein E, tissue inhibitor of metalloproteinase-3 (TIMP-3), immunoglobulins-under RPE [38]. Dysfunction of RPE which occurs progressively leads to the creation of a toxic environment (such as the brain), this, in turn, increases oxidative stress, alters lipid metabolism, and results in accumulation of toxic products from heterophagy [39,40].

The chronicity of these events leads to the perpetuation of a pro-inflammatory environment with the final result being extensive damage to the RPE and photoreceptors. As a compensatory mechanism, RPE tries to amplify the antioxidant response and promote autophagy. Despite this fact, there is a progressive deregulation of RPE associated with an oxidative burden which makes these mechanisms unable to make up for the effects of pro-inflammatory and pro-oxidative cascades [21,26]. The increased levels of cytokines and inflammatory molecules discovered in patients with atrophic AMD support this theory.

In patients with geographic atrophy, the higher levels of IL-17, IL-6, TNF2 receptor and C-reactive protein was found compared to the control group, correlating with the progression rate of atrophy [37,41].

A 2018 study, which measured cytokines levels in the aqueous humor of some patients with atrophic AMD, highlighted an increased level of CXCL5 (C-X-C chemokine ligand 5), CXCL6 (C-X-C chemokine ligand 6) and MIG/CXCL9, thus being relevant to the implication of T lymphocytes in the pathological mechanisms behind AMD [37,42].

The complement cascade, activated by 3 different pathways, promotes the clearance of apoptotic cells through their opsonization, to be removed by phagocytosis [25]. Furthermore, multiple histological and biochemical analyses of drusen have highlighted the presence of the factors involved in the complement cascade as major constituents of drusen [43]. Significantly high plasma levels of C3d, C3a, C5a have been reported in patients with AMD [43,44].

Inflammation and exudative AMD

As in the case of atrophic AMD, inflammation at the local level is responsible for the RPE degradation and the degeneration of the outer segments of the photoreceptor cells [24].

The formation of new blood vessels can be classified into angiogenesis and vasculogenesis [45]. Vasculogenesis involves the appearance of new vessels that occurs mainly during embryogenesis. Angiogenesis is responsible for the emergence of new vascular plexuses from pre-existing blood vessels, being a key process in the development and regeneration of tissues; proangiogenic factors stimulate it, being in a close relationship with inflammation [45,46].

During the acute inflammatory phase, immune cells and fluid cumulate at the inflammatory site, a process due to the changes in the integrity of the small vessels [13,45]. The damaged cells express molecules known as damage-associated molecular patterns (DAMP) which are recognized by the PRR inducing the amplification of the response immune [13]. Proinflammatory cytokines are released (IL-1β, IL-6, IL-17, TNF-α, TGF-β), which in turn activate endothelial cells, producing vasodilation and increased vascular permeability [45]. Activation of endothelial cells is characterized by the increase in the expression of molecules for leukocyte adhesion, the production of new cytokines, and growth factors, all leading to changes at the level of pericytes, further altering the retinal microenvironment [13,30,45]. In addition to the pro-inflammatory role of cytokines present at the level of the RPE, they act as proangiogenic factors. The most important cytokines with a proangiogenic role are: IL-1β, IL-6, IL-17, TNF-α, TGF-β, MCP-1, MIP-1α, VEGF [37].

IL-17 promotes angiogenesis through its effect on CXCL8 and CCL2 [37,47]. TNF-α increases VEGF production by activating a pathway dependent on reactive oxygen species [48]. VEGF, the most important factor responsible for the appearance of choroidal neovascularization, has been extensively studied and is currently the target of treatment in patients with choroidal neovascularization [7,32]. At the retinal level, VEGF is found in several isoforms: VEGF-A - the most studied isoform, stimulates angiogenesis and increases vascular permeability and VEGF-B- the exact role it plays in AMD pathogenesis is not known, however, one of the most used drugs (Aflibercept) targets this isoform. VEGF-C and VEGF-D are involved in regulating the growth of lymphatics, and contribute to the promotion of inflammation and angiogenesis [6]. PLGF-placental growth factor (placental growth factor), interacts with VEGF-A and contributes to neovascularization [49-51].

VEGF selectively stimulates endothelial cells, binding to specific receptors: VEGFR-1, VEGFR-2, and VEGF-3,

which activate a variety of mechanisms [50,51]. First of all, it stimulates angiogenesis, being a potent mitogen for endothelial cells and it supports cell survival by repressing apoptosis [32,51]. VEGF is a chemoattractant for precursors of endothelial cells, stimulating their differentiation [51]. It increases vascular permeability, most likely through the formation of fenestrations at the level of the endothelium [32,52]. VEGF can also promote angiogenesis through an indirect mechanism - by degrading the components of the extracellular matrix [32,53].

Other growth factors involved in angiogenesis, resulting from inflammatory processes at the RPE level, are angiopoietin 1 (ANG-1) and angiopoietin 2 (ANG-2) [44,54]. ANG-1 interacts with the endothelial tyrosine-kinase receptor Tie-2 inhibiting vascular leakage and inflammation [44,55]. ANG-2 acts as a competitive antagonist of ANG-1, its expression is increased in exudative AMD, thus contributing to the angiogenesis process [54-57].

Also, several other inflammatory cytokines can contribute to the appearance of neovascularization. IL-1β, IL-12, IL-23, interferon-γ, and TNF-α can activate M1-type macrophages, having a considerable pro-inflammatory effect [37,58]. We can postulate that the inflammation induced by degenerative processes at the retinal level acts as a stimulus for the migration of M1 macrophages in the retina, which under the influence of Rho-kinases convert into M2 type macrophages, creating ideal proangiogenic conditions [59-61].

Conclusions

Multiple mechanisms are involved in AMD pathogenesis, including the inflammatory one, being a major cause of disease progression. Therapies available for both the atrophic and the exudative form target certain cytokines involved (VEGF, the C3 fraction of the complement). Even though the intended effect should be anti-inflammatory, many of these substances produce a significant degree of intraocular inflammation, which indicates the possibility of the involvement of other molecules that require additional investigations. Even if the biochemical profile of the various molecules involved is known, it varies with the stage of the disease. Moreover, there are currently no studies that correlate the values of different inflammatory biomarkers with the response to treatment. The possibility of developing a pro-inflammatory profile of the patient will help in adjusting the treatment to improve both the safety profile and the result.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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