Charles University

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Study programme: Biology

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Characterization of immunopathological processes involved in development of age-related macular degeneration

Charakterizace imunopatologických procesů podílejících se na rozvoji věkem podmíněné makulární degenerace

Bachelor´s thesis

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Declaration/Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu. Dále prohlašuji, že umělá inteligence byla využita pro drobné stylistické a gramatické úpravy textu.

V Praze, 22.4.2025 Yujune Lee

Abstract

Age-related macular degeneration (AMD) is one of the leading causes of vision loss. Its development is associated with complex immunopathological processes in the retina, involving chronic inflammation and dysregulation of retinal immune homeostasis. The inflammatory response in AMD involves several key components, such as the complement system, microglia, macrophages, mast cells, T lymphocytes, and associated alterations in the production of cytokines. This thesis explores current therapeutic options for AMD and future perspectives in its treatment. Advances in immunotherapy and immune cell modulation offer promising options for developing more effective and targeted treatment strategies that aim to restore immune balance in the retina.

Key words: age-related macular degeneration, microglia, macrophage, monocyte, mast cell, T-lymphocyte, complement system, cytokine, retina, choroidal neovascularization

Abstrakt

Věkem podmíněná makulární degenerace (VPMD) patří v současnosti mezi jednu z hlavních příčin ztráty zraku. Za jejím vznikem stojí kaskáda imunopatologických procesů probíhajících v sítnici včetně chronického zánětu a narušení lokální imunitní homeostázy. Na rozvoji zánětlivé reakce u VPMD se podílí mimo jiné komplement, mikroglie, monocyty, makrofágy, žírné buňky, T-lymfocyty a s tím související změny v produkci cytokinů. Práce se zabývá současnými možnostmi terapie VPMD a perspektivou její léčby do budoucna. Pokroky v oblasti imunoterapie a modulace imunitních buněk přinášejí naději pro vývoj účinnějších a cílenějších léčebných strategií, které mohou přispět k obnovení imunitní rovnováhy v sítnici.

Klíčová slova: věkem podmíněná makulární degenerace, mikroglie, makrofág, monocyt, žírná buňka, T-lymfocyt, komplementový systém, cytokiny, sítnice, choroidální neovaskularizace

List of abbreviations

ACAID	anterior chamber-associated immune deviation
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
ATP	adenosine triphosphate
ATR1	angiotensin II type-1 receptor
BM	Bruch‘s membrane
BRB	blood-retinal barrier
CC	choriocapillaris
CCL2	C-C motif chemokine ligand type 2
CCR2	C-C chemokine receptor
CD	cluster of differentiation
CFH	complement factor H
CNV	choroidal neovascularization
CRP	C-reactive protein
CXCL	C-X-C motif ligand
DAMPs	damage-associated molecular patterns
ECM	extracellular matrix
FGF	fibroblast growth factor
GA	geographic atrophy
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
Ly6C	lymphocyte antigen 6, locus C
α-MSH	α-melanocyte-stimulating hormone
nAMD	neovascular age-related macular degeneration
NLRP3	NLR family pyrin domain containing 3
NR4A1	nuclear receptor 4A1
PDGF	platelet-derived growth factor
Prf1	perforin-1
RPE	retinal pigment epithelium
Tc	cytotoxic T cell
Th	helper T cell
TGF	transforming growth factor
TLR	toll-like receptor
TNF	tumor necrosis factor
Treg	regulatory T cell
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

Outline

1 Introduction

Age-related macular degeneration (AMD) represents a leading cause of irreversible blindness in developed countries, with a primary impact on the elderly population. It is estimated that 196 million people suffer from AMD worldwide. The disease is characterized by the degeneration of the macula, the region in the retina responsible for central vision. AMD is a complex and multifactorial disease, involving contributions from genetic predisposition, environmental factors, and dysregulated immune responses.

The primary risk factor associated with AMD is aging. However, lifestyle factors such as smoking and insufficient dietary intake of antioxidants, like zinc and carotenoids, also contribute significantly to disease onset and progression. AMD affects the various types of cells in the macula, particularly retinal pigment epithelium (RPE) cells, Bruch's membrane (BM), and the choriocapillaris (CC), which all support photoreceptor function. Disruption in these structures initiates chronic inflammation, pathological immune cell activation, and progressive retinal degeneration. Recent research shows that immune dysregulation is recognized as a key factor in the pathogenesis of AMD, particularly through the uncontrolled activation of microglia, macrophages, and complement system components. Given the demographic shift towards an aging global population, understanding the immunopathological mechanisms driving AMD is of growing importance.

The progression of the disease can be slowed down by the administration of high-dose zinc and antioxidant vitamin supplements. Additionally, intravitreal anti-vascular endothelial growth factor (VEGF) therapy has demonstrated efficacy in the treatment of neovascular AMD (nAMD), resulting in a significant reduction in the prevalence of visual impairment worldwide. For non-neovascular AMD, a drug called pegcetacoplan has been recently approved. However, both the anti-VEGF therapy and pegcetacoplan are confronted with certain challenges.

Comprehension of the immunopathological mechanisms underlying AMD is essential for the development of innovative therapeutic strategies. This thesis aims to characterize the immune-related processes involved in the pathogenesis of AMD, with a particular focus on pro-inflammatory reaction, complement system dysregulation, and immune cell interactions.

2 Structure of the eye

The human eye is a complex sensory organ that consists of an anterior and a posterior segment (see Figure 1). The anterior segment, which includes the cornea, iris, ciliary body, lens, and aqueous humor, contributes to light focusing, intraocular pressure regulation, nutrient delivery, and waste clearance. The posterior segment contains the retina, choroid, optic nerve, and vitreous humor. The retina is a neurosensory tissue responsible for phototransduction. The choroid, a vascular layer situated between the retina and sclera, supplies the retina with vital nutrients, ensuring its functionality. Phototransduction is the process by which photoreceptor cells in the retina convert light into electrical signals. The light passes through the cornea and then travels through the aqueous humor, the pupil, the lens, and the vitreous humor to reach the retina. The first cells exposed to the incoming light are the ganglion cells, located on the inner surface of the retina. Then the light passes through bipolar cells, Müller glial cells, and finally reaches photoreceptor cells, which are responsible for converting light into electrical signals. These signals are transmitted into the brain via the optic nerve, enabling visual processing (*Suri, Beg, Kohli, 2020; *Willoughby et al. 2010).

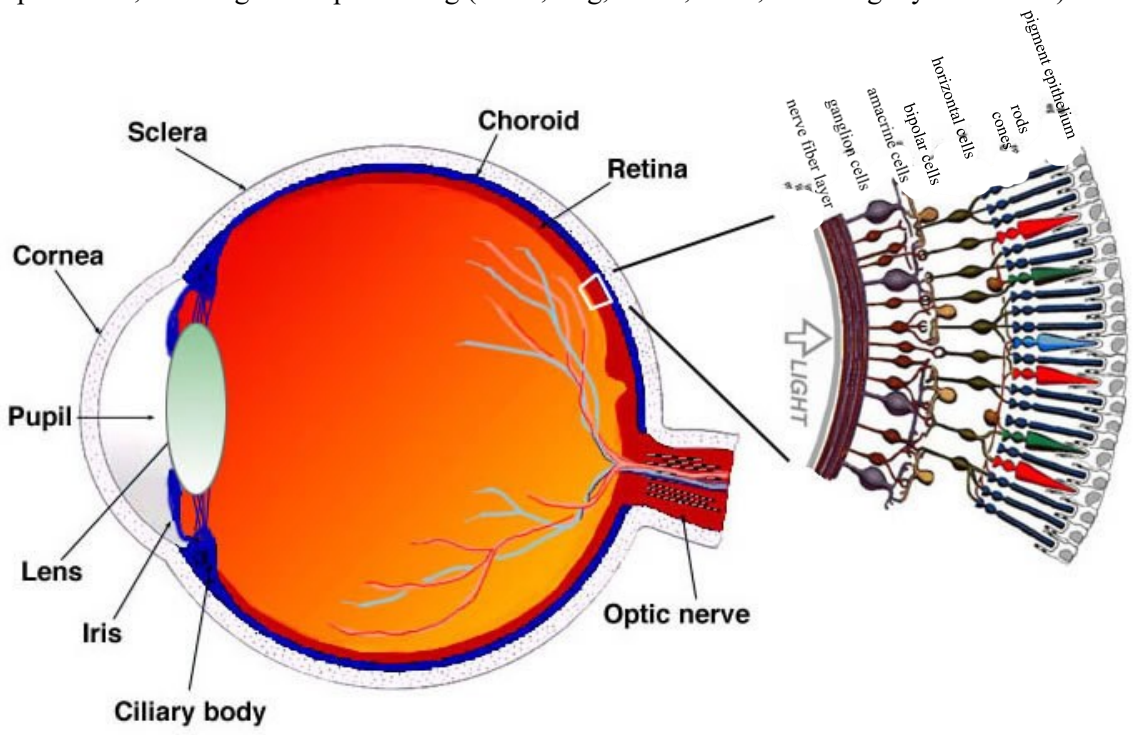

Figure 1: Structure of the eye. The left panel shows a cross-sectional view of the eye with the key structures of the eye. The right panel provides a detailed view of the retinal cellular organization (adapted from *Kolb, 2012, with modifications).

2.1 The retina

The vertebrate retina is composed of seven major cell types. The outer nuclear layer contains photoreceptors that are attached to the RPE. The inner nuclear layer consists of bipolar, horizontal, and amacrine cells, which transmit visual information from photoreceptors to ganglion cells. The ganglion cell layer acts as the retina's output neurons by transmitting visual information to the brain via the optic nerve. Müller glial cells maintain retinal structure and homeostasis. They are capable of reentering the cell cycle in response to retinal injury or disease to restore damaged cells. Additionally, the retina contains astrocytes, microglia, and vascular cells (Bernardos et al. 2007; *Stenkamp, 2015).

Several key structures are fundamental to understanding the mechanisms underlying retinal disease, such as AMD. These include the photoreceptors, the RPE, the BM, the CC, and the macula.

The photoreceptors, which are specialized neurons that detect light and initiate the transmission of signals, are categorized into rods and cones. Rods are highly sensitive and respond to low light. On the contrary, cones are responsible for color vision and require greater light intensity. The human retina contains three types of cones, each sensitive to a specific range of light wavelengths (*Bhutto, Lutty, 2012; *Malhotra et al. 2011).

The RPE directly interacts with the photoreceptors with its apical surface, and on the basolateral side, is attached to the BM (*Malhotra et al. 2011). Their anterior region is filled with melanosomes, absorbing the excess light, and has finger-like extensions that reach between the photoreceptor outer segments. The RPE cells are part of the blood-retinal barrier (BRB), supply essential nutrients, and are responsible for removing metabolic waste from the photoreceptors and the choroid via phagocytosis. They also produce various growth factors, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and most importantly AMD AMD-relevant VEGF (*Bhutto, Lutty, 2012).

BM is a thin extracellular matrix (ECM), composed primarily of collagen and elastin. It serves as a selective barrier, regulating the movement of nutrients, waste, and signaling molecules between the CC and RPE. Furthermore, it provides structural support to keep RPE cells anchored, offers a surface for RPE cell migration and differentiation, and contributes to wound healing (*Fields et al. 2020).

The CC is a network of capillaries located in the choroid, with the fenestration on the posterior side, facilitating the efficient exchange of nutrients, oxygen, and waste with the retina. These cells express VEGF receptors (VEGFR), a receptor that plays a role in regulating blood vessel dynamics, and intercellular adhesion molecule-1, a protein that helps immune cells to adhere to the blood vessel walls (*Fields et al., 2020; *Willoughby et al. 2010).

The macula, located at the center of the retina, is essential for high-acuity vision. The fovea centralis is an area in the macula with the highest density of cone photoreceptors, specialized for sharp central vision (*Willoughby et al. 2010).

3 AMD

3. 1 Types

AMD can be classified into 3 distinct stages (early, intermediate, late) based on the size and characteristics of drusen, which are extracellular deposits that accumulate between the RPE and BM (see Figure 2). Drusen serve as key biomarkers in assessing AMD progression, with their size, localization, quantity, and associated pigmentary changes helping to determine disease severity (Gotfredsen et al. 2025). Late AMD is characterized by the presence of lesions, which result in atrophy of the outer retina, thinning and loss of the RPE, and choroidal neovascularization (CNV). This condition is commonly associated with visual loss. The pathological progression of late AMD can be subdivided into two distinct subtypes: nAMD and geographic atrophy (GA) (Spaide et al. 2020; Ferris et al. 2013).

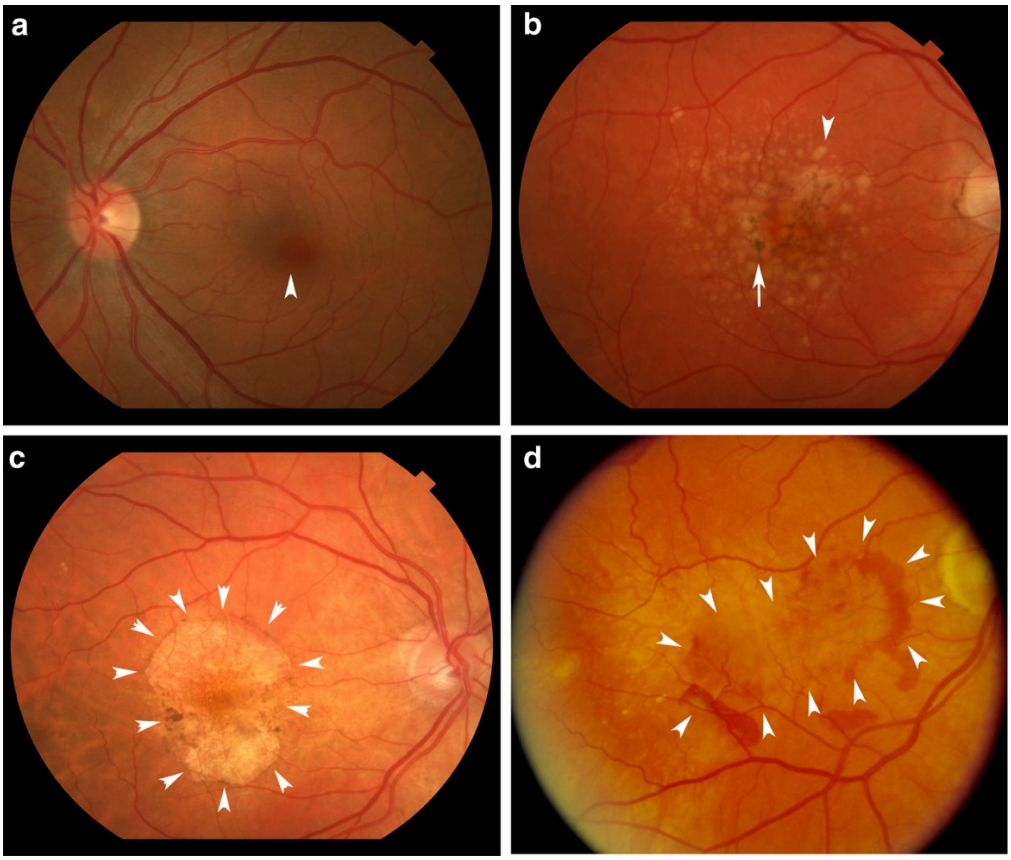

Figure 2: Fundus photography comparison. Picture (a) shows a normal macula in the healthy eye. Picture (b) shows intermediate AMD, where the arrowhead points to a large druse while the arrow points at the hyperpigmentation of the RPE. Picture (c) represents a geographic atrophy. In the picture (d), arrowheads outline the CNV area (*Handa et al. 2019).

3.1.1 nAMD (wet AMD, exudative AMD)

Wet AMD is less common than GA but is responsible for 90% of the severe vision loss in patients affected by AMD (*Pugazhendhi et al. 2021). It is characterized by CNV that grows into the outer retina, subretinal space, or sub-RPE space. CNV may have a partially protective role by attempting to restore oxygen and nutrient supply to the retina when the CC is deficient (Joyal et al. 2017). However, in most cases, CNV results in leakage, bleeding, scarring, and severe vision loss that is more acute than dry AMD (Salas et al., 2023).

Exudation, resulting from CNV, refers to the leakage of fluid caused by abnormal blood vessel growth. It can be manifested in four distinct forms: (1) leakage – characterized by the breakdown of the blood-ocular barrier, resulting in fluid escape (2) accumulation of intraretinal and subretinal fluid (3) accumulation of fatty deposits (4) accumulation of hyperreflective material, such as serum, fibrin, and inflammatory cells under the retina.

Additional components of CNV include: (1) RPE detachment from fluid, blood, or fibrous tissue buildup (2) hemorrhage from abnormal vessels (3) fibrosis from neovascularization (4) RPE tears due to fibrovascular traction (Spaide et al. 2020).

Optical coherence tomography imaging is used to determine the location of the neovascular growth, and it helps to subclassify the disease (Amissah-Arthur et al. 2012). Type 1 CNV involves choroidal vessels invading the sub-RPE space (Faatz et al., 2022). A subtype of type 1 CNV is called polypoidal choroidal vasculopathy. It is more common in the Asian population and is featured by branching nodules (polyps) (Tan et al., 2018). Type 2 CNV occurs when choroidal vessels grow through RPE, causing fluid leakage and severe vision loss. Type 3 CNV originates from the retinal circulation, forming tangled vessel networks that lead to swelling, cysts, fluid accumulation, scarring, and progressive vision loss (Faatz et al., 2022).

3.1.2 GA (dry AMD, non-neovascular AMD, atrophic AMD, non-exudative AMD)

Atrophy in the context of AMD refers to the irreversible loss of tissue due to progressive degeneration of the RPE, photoreceptors, and CC. Dry AMD is characterized by the thickening of the BM, primarily caused by the accumulation of drusen (Davis et al. 2005). These deposits also act as both mechanical and chemical barriers, disrupting the interaction between the RPE and the underlying choroid (Mullins et al. 2011).

GA is one of two advanced stages of AMD and is defined as round or oval areas of pigmentation abnormalities with increased visibility of the underlying choroidal vessels, typically measuring 175 micrometers in diameter (Sadda et al. 2018). These lesions often begin in the non-foveal retina, preserving visual acuity. However, as the disease progresses to the fovea, it potentially results in blindness within 3.3 to 8.5 years (Chakravarthy et al. 2018). Additionally, GA can coexist with nAMD, further complicating disease development (Dhrami-Gavazi et al. 2015).

3.2 Pathophysiology

The pathogenesis of AMD is characterized by changes in the RPE, BM, and CC affecting primarily the macula. These three structures are interdependent, therefore, any damage to one component invariably compromises the functionality of the others. For instance, RPE damage compromises photoreceptor support, CC damage reduces RPE blood supply, and BM dysfunction follows RPE degeneration (*Al-Zamil, Yassin, 2017; *Bhutto, Lutty, 2012).

The RPE contains non-dividing cells that undergo several changes during the process of aging, including a decline in melanosomes, which results in a reduction of protection against light-induced damage. RPE cell density decreases with age, and this effect is associated with weakened support for photoreceptors, and lipofuscin accumulation promoting oxidative stress (*Goodman, Ness, 2023). The presence of small drusen, focal yellow deposits of extracellular material without other ocular abnormalities, is commonly seen as a part of the normal aging process. However, when waste clearance becomes impaired, larger drusen and pigmentary abnormalities may develop, indicating underlying pathology (*Al-Zamil, Yassin, 2017). In early AMD, RPE morphology changes, resulting in the damage of cells in advanced stages (*Bhutto, Lutty, 2012). These alterations in RPE trigger oxidative stress and accumulation of waste between the RPE and BM. Factors like blue light exposure, high oxygen demand, and low antioxidants worsen oxidative stress. In addition, lipofuscin generates reactive oxygen species and causes RPE cell death (*Różanowska, 2023).

BM goes through a process of thickening of the collagenous layers with advancing age. Over time, the structural components of BM, elastin, and collagen begin to degenerate. BM can also undergo calcification, reducing its flexibility. These changes impair the efficient transport of nutrients and waste, which can trigger an accumulation of oxidative stress that contributes to the development of dry AMD (*Al-Zamil, Yassin, 2017).

Aging causes CC thinning, which reduces blood flow and contributes to inefficient removal of waste products, promoting drusen accumulation. Loss of CC leads to ischemia, which triggers VEGF production and promotes the growth of abnormal choroidal vessels, potentially progressing from dry AMD to wet AMD. Inflammation further drives angiogenesis, as macrophages and inflammatory cells release cytokines that promote new vessel formation. New blood vessels penetrate the BM and then extend beneath the RPE. However, these newly formed blood vessels are dysfunctional, causing blood leakage and hemorrhage. As a result, in the final stage of wet AMD, these vessels form a disciform scar, which causes irreversible damage to the central vision (Biesemeier et al. 2014; Coco, Sala-Puigdollers, 2014; Mullins et al. 2011).

The precise mechanism underlying the increased susceptibility of the macula to degeneration is unclear, but certain factors provide insight. The BM is thinner and more porous in the macula compared to the rest of the retina. These features are vital for BM's role in transporting molecules between the choroid and the RPE, but may also facilitate CNV. The macula's high concentration of cones places considerable metabolic and phagocytic demands on RPE cells. This can result in the accumulation of undigested

materials, including drusen and lipofuscin, both of which are associated with the progression of AMD (Chong et al. 2005; Volland et al. 2015).

3.3 Epidemiology

AMD is a leading cause of central vision loss in developed countries. The condition primarily affects the elderly population, with its prevalence increasing significantly with age (*Wong et al. 2014)

The global prevalence of AMD was about 196 million affected individuals in 2020. AMD accounts for 8.7% of all cases of blindness worldwide, ranking as the second leading cause of irreversible blindness in 2020 (Furtado et al. 2024; *Wong et al. 2014; Zhou et al. 2025). The atrophic form accounts for 85-90% of cases, while the exudative form accounts for 10-15% (Volland et al. 2015). It's important to note that atrophic AMD cases can progress to the more severe nAMD (*Bhutto, Lutty, 2012). The number of AMD cases is projected to rise dramatically due to population aging. The prevalence is predicted to increase by 2040 to 288 million people (*Wong et al. 2014).

3.4 Risk factors

AMD is a complex disease influenced by both genetic and environmental factors, with aging representing the most significant risk factor. Several AMD severity scales have been developed to monitor disease progression at earlier stages, such as the Age-Related Eye Disease Study (AREDS) scale (Klein et al. 2014). The AREDS scale classifies AMD severity into 4 grades, from no AMD (Grade 1) to late AMD (Grade 4). The AREDS Simplified Risk Scale assesses risk based on retinal abnormalities, such as large drusen and pigmentary changes, with a scoring system ranging from 0 (no risk) to 4 (high risk). However, genetic and environmental factors modify this scale (Ferris et al. 2013; 2005).

Non-modifiable risk factors include genetic variants affecting the complement system, ECM remodeling, and lipid metabolism. The complement factor H (CFH), particularly the Y402H polymorphism, has been shown to increase the risk of AMD (Keenan et al. 2020). Other significant genetic factors associated with AMD include the Age-related maculopathy susceptibility 2 and high-temperature requirement A serine peptidase 1 genes, both located on chromosome 10q26. Their influence on ECM function correlates with an increased risk of AMD (Yu et al. 2012).

Smoking increases the risk of AMD by two- to fourfold (Jonasson et al. 2014), while a Mediterranean diet rich in antioxidants can reduce the risk of late AMD by up to 60% (Keenan et al. 2020; Barreto et al. 2023). The AREDS and AREDS2 studies found that supplements containing vitamin C and E, lutein, zeaxanthin, zinc, copper, and omega-3 fatty acids help lower AMD risk (Chew et al. 2022).

3.5 Current therapy

Although treatment options are available to decrease the symptoms, there are currently no effective therapies to prevent the underlying disease mechanisms. This is due to the highly complex nature of the disease, which involves multiple cellular abnormalities contributed by local inflammation and the influx of peripheral leukocytes into the retina (*Nanegrungsunk et al. 2022).

One of the most prevalent treatment modalities for nAMD is anti-VEGF therapy. This therapeutic intervention has demonstrated efficacy in stabilizing the disease process and, in some cases, even reversing symptoms (Thomsen et al. 2024). Anti-VEGF drugs function by blocking VEGF, a protein that plays a pivotal role in pathological angiogenesis. The introduction of anti-VEGF therapy in 2006 has been shown to reduce the number of disease progression (Cheema et al. 2021). Despite the significant efficacy of anti-VEGF, the response to therapy considerably varies. The partial or absent response to the treatment may be caused by a dysregulated complement system. Frequent injections burden patients and healthcare systems (Thomsen et al. 2024), and the treatment does not prevent complications such as GA (Grunwald et al. 2016) or subretinal fibrosis (Daniel et al. 2013). Anti-VEGF is insufficient for long-term disease control, and the therapy doesn't result in the complete cure of the underlying disease (Cheema et al. 2021).

The first treatment for GA, pegcetacoplan, blocks the complement system but only slows disease progression without curing it. Similarly to the application of anti-VEGF therapy, it requires ongoing and frequent injections (Heier et al. 2023; Nittala et al. 2022). For patients diagnosed with either dry or wet AMD, a set of recommended lifestyle modifications has been established. These modifications include maintaining a balanced diet, the use of AREDS and AREDS2 supplements, and the termination of smoking to slow disease progression (Jonasson et al. 2014; Keenan et al. 2020; Barreto et al. 2023; Chew et al. 2022).

4 Role of the immune system in the development of AMD

The eye is a highly specialized organ that requires a balance between immune defense and suppression to maintain function and protect its structures. Several regulatory mechanisms ensure an anti-inflammatory microenvironment, preventing excessive immune responses that could harm tissues (*J. Wayne Streilein, 2003). The retina, as an extension of the central nervous system, is an immune-privileged site designed to limit inflammation and protect its low-regenerative neurons (Schafer et al. 2012). However, when these regulatory systems fail, uncontrolled immune responses can contribute to retinal diseases such as AMD, leading to progressive damage and vision loss. Drusen accumulation in the subretinal space triggers chronic low-grade immune inflammation, also referred to as para-inflammation, which is mainly driven by the complement system. This results in the activation of microglia, the formation of inflammasomes, and the recruitment of monocytes and macrophages (*Whitcup et al. 2013).

4.1 The regulation of immune cells in the retina

Several mechanisms contribute to immune privilege, including the BRB and immunosuppressive factors that prevent excessive inflammation. The inner BRB is primarily composed of retinal endothelial cells and their tight junctions. The outer BRB, formed by RPE cells joined by tight junctions, limits the transmission of inflammatory mediators and the infiltration of immune cells (see Figure 3) (Ivanova et al. 2019).

Beyond physical barriers, immunosuppressive factors such as interleukin (IL)-10, transforming growth factor (TGF)-β, and α-melanocyte-stimulating hormone (α-MSH) are secreted by the RPE and immune cells to regulate inflammation and support regulatory T cells (Tregs). This immunoregulatory environment is further reinforced by anterior chamber-associated immune deviation (ACAID), which enhances immune tolerance via Tregs and anti-inflammatory cytokines (*J. Wayne Streilein 2003; *Wang et al. 2023). Additionally, Fas ligand and programmed death-ligand 1 on RPE cells inhibit inflammatory T cells, maintaining retinal homeostasis (Ke et al. 2010).

The complement system is continuously activated at low levels in the normal eye, strictly regulated by intraocular complement regulatory proteins, such as CFH (Weismann et al. 2011). These mechanisms collectively preserve immune balance, preventing inflammation while allowing for controlled immune responses when needed (*Zhu, Hong, Zhou, 2023).

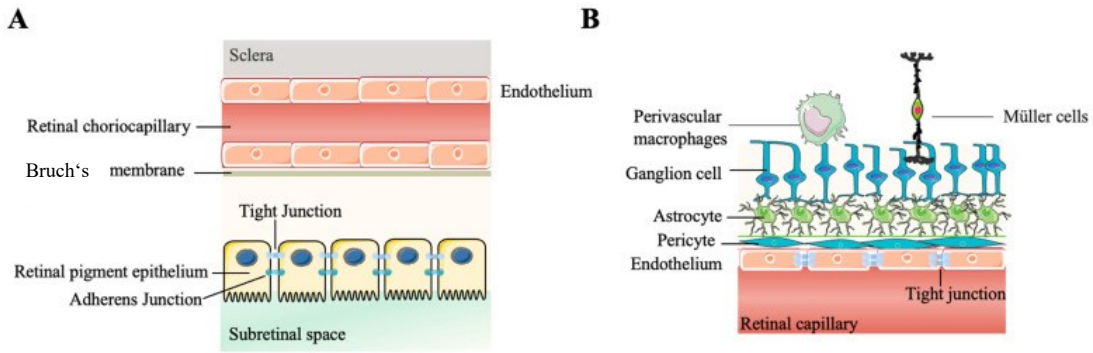

Figure 3: Blood-retinal barrier. The picture A shows outer BRB, which is formed by the RPE. The picture B shows inner BRB, which is composed of the CC and BM (adapted from *Wang et al. 2023, with modifications).

4.2 Immunocompetent cells in the healthy and diseased retina

In a healthy eye, immune cells like microglia and macrophages are kept in an immunosuppressive state through immune privilege mechanisms, playing an essential role in immune surveillance, suppressing immune reactions, and promoting tolerance to preserve retinal function (*J. Wayne Streilein 2003; *Wang

et al. 2023). Mononuclear phagocytes, including monocytes, monocyte-derived inflammatory macrophages, dendritic cells, and tissue-resident microglia, are the key drivers of AMD pathogenesis (Roubeix et al. 2024).

The diseased retina is characterized by increased cytokine production, immune cell infiltration, increased BRB permeability, and chronic inflammation. This chronic inflammation is a key contributor to the development and progression of CNV. The choroid, where macrophages and mast cells are most abundant in AMD patients, becomes a major site of inflammatory activity (Bhutto et al. 2016; Nagai et al. 2006). Genetic variants related to AMD (CFH Y402H and 10q26 haplotype) directly increase the number of mononuclear phagocytes in the subretinal space (Beguier et al. 2020)

4.2.1 Microglia

Microglia are specialized macrophages that serve as the primary immune cells in the central nervous system, including the retina. They are distributed across distinct retinal layers, including the nerve fiber layer/ganglion cell layer, and the inner and outer plexiform layers (McMenamin, Polla, 2013; *Reichenbach, Bringmann, 2020). Microglia play a role in maintaining retinal immune homeostasis by clearing synapses and debris (Stevens et al. 2007). In the healthy eye, microglia's activity is suppressed by negative regulators such as α-MSH produced by RPE cells and a cluster of differentiation (CD) 200 expressed on the surface of neural and epithelial cells (Copland et al. 2007; *Wang et al. 2023). The resting microglia contribute to the anti-inflammatory state of the retina. Unlike other antigen-presenting cells, microglia express low levels of major histocompatibility complex class II, limiting their ability to activate T cells and thereby helping maintain an ocular immune privilege (Taylor, Ng, 2018). Additionally, these resident immune cells continuously monitor the environment and respond to tissue damage and pathogens with strictly regulated immune activity. Microglia are the only phagocytes able to migrate into the subretinal space, maintaining immune homeostasis by secreting anti-inflammatory molecules like TGF-β2, IL-10, and interferon (IFN)-β (*Reichenbach & Bringmann 2020; O'Koren et al. 2019). However, under pathological conditions such as AMD, these immune cells become dysregulated, and microglia and macrophages accumulate in the subretinal space, where they secrete pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) that trigger chronic inflammation and contribute to retinal degeneration (Zhou et al. 2017).

Microglia exhibit two polarized phenotypes (see Figure 4). The M1 phenotype secretes pro-inflammatory factors such as tumor necrosis factor (TNF)-α, IL-1β, and IL-6, which can damage the retina and disrupt the BRB. In contrast, the M2 phenotype has anti-inflammatory properties and can transform from the M1 phenotype in response to signals such as TGF-β1, IL-4, and IL-10. When M1 microglia dominate, inflammatory pathways become overactive, and tight junctions of the BRB are disrupted (Fang et al. 2021; Zhou et al. 2017).

Adult microglia exhibit a highly ramified morphology that facilitates communication with various retinal cells, such as photoreceptors, retinal ganglion cells, Müller cells, and endothelial cells. This

interaction is mediated through molecules like CD200 and fractalkine, which is also known as chemokine C-X3-C motif ligand 1. Fractalkine signaling is crucial for the migration of microglia, promoting tissue repair. It was shown that the expression of the receptor for fractalkine is lower in nAMD patients in comparison to healthy individuals, while the levels of fractalkine remained unaltered. This finding suggests that the disease progression is caused by a reduced ability of immune cells to detect and respond to chemotactic signals (Copland et al. 2007; Falk et al. 2014; Mills et al. 2021).

Microglia become activated in response to cellular damage, infection, or para-inflammation. This process is influenced by intraocular cytokines and signals from the RPE (*Zhu, Hong, Zhou, 2023). Microglia detect damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns via pattern recognition receptors, such as Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain-like receptors, retinoic acid-inducible gene-I-like receptors, C-type lectin receptors, complement factors, and many other receptors. The DAMPs are produced by damaged, dead, stressed cells or by drusen. Among DAMPs are included Alu ribonucleic acid, amyloid β oligomers from drusen, fibrinogen, lipid oxidation products, adenosine triphosphate (ATP) released from dying cells, high mobility group protein B1 released by damaged photoreceptors, and cathepsin released from RPE (*Brandli, Vessey, Fletcher, 2024; *Wang et al. 2023). Additionally, ATP signaling plays a role in microglial activation and retinal degeneration. ATP is released by necrotic cells or in the early phase of apoptosis. In animal studies, intravitreal injection of ATP has been shown to induce photoreceptor apoptosis through activation of the P2X7 receptor. ATP released into the subretinal space after retinal detachment triggers microglial pyroptosis via P2X7 receptor activation, further exacerbating photoreceptor damage (Cao et al. 2023).

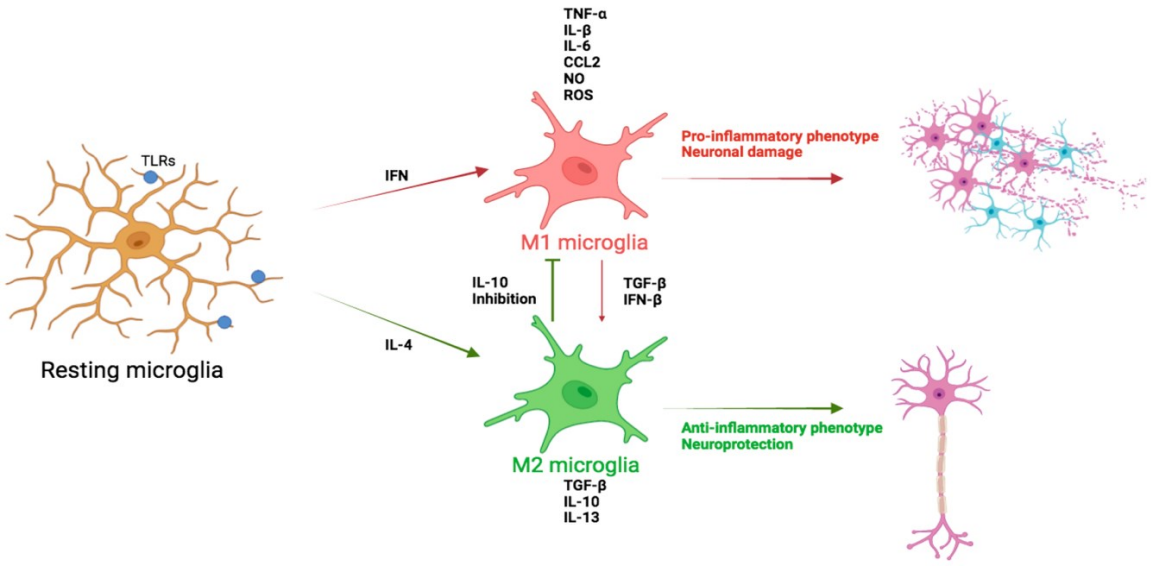

Figure 4: Microglial polarization and the relationship between M1 and M2 microglial phenotypes. Resting microglia express TLRs and become activated in response to cytokines. The M1 phenotype is pro-inflammatory, while the M2 phenotype is neuroprotective (*Ana, 2024).

Upon activation, microglia undergo significant morphological and functional changes. They become more migratory, proliferative, and phagocytic. The phagocytosis of apoptotic neurons is mainly mediated by triggering receptors expressed on myeloid cells-2 (Kim et al. 2017). They release pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, and TNF-α, along with chemokines and neurotrophic factors (Fang et al. 2021; Zhou et al. 2017). While short-term activation can be protective, promoting the clearance of damaged cells and pathogens, prolonged or chronic activation leads to harmful neuroinflammation (Ronning, Karlen, Burns, 2022). To regulate inflammation, microglia upregulate a translocator protein that interacts with its ligand, the diazepam-binding inhibitor, which is released by astrocytes and Müller cells. This interaction serves to regulate microglial activation and prevent excessive inflammation (Karlstetter et al. 2014). However, under chronic inflammatory conditions, the BRB may be compromised, allowing monocyte-derived macrophages to infiltrate the retina, further contributing to disease progression (Fang et al. 2021). The activity of microglia is also linked to retinal vascular function, secreting trophic and angiogenic factors. These factors facilitate the rapid removal of excess vascular debris and control vessel diameter and blood flow (Mills et al. 2021). In nAMD, activated microglia accumulate in the subretinal space, where they contribute to pathological vascular proliferation by releasing proangiogenic factors such as VEGF, PDGF-β, FGF-1, FGF-2, and TGF-β1. These factors promote abnormal blood vessel formation, which is a hallmark of this condition (*Wang et al. 2023).

4.2.2 Monocytes

Mononuclear phagocytes originate from hematopoietic cells in the bone marrow and differentiate into monocytes, macrophages, and dendritic cells, which all contribute to photoreceptor damage and CNV. The increased levels of C-C motif chemokine ligand type 2 (CCL2), a monocyte-attracting factor, were found in the eyes of patients with advanced AMD (Sennlaub et al. 2013). Under normal conditions, monocytes from peripheral circulation do not infiltrate the central nervous system, unless the BRB is compromised (Fang et al. 2021).

Hematopoietic stem cells differentiate into C-C motif chemokine receptor type 2 (CCR2) positive and lymphocyte antigen 6 locus C (Ly6C) high positive ($CCR2^{+}Ly6C^{high}$) cells (classical monocytes) and eventually into $CCR2^{-}Ly6C^{low}$ cells (non-classical monocytes) in the blood (Roubeix et al. 2024) under the influence of transcription factor nuclear receptor 4A1 (NR4A1). NR4A1 deficiency resulted in the absence of non-classical monocytes and the recruitment of pro-angiogenic macrophages. Mice lacking the CCR2 gene show reduced CNV, similar to what happens when macrophages are completely removed, proving their pathological role (Droho et al. 2023b).

It has been established that some classical monocytes accumulate in the splenic reservoir and convert into splenic monocytes positive for angiotensin II type-1 receptor (ATR1). In the presence of pathological conditions, $ATR1^{+}$ and classical monocytes undergo differentiation into inflammatory monocyte-derived cells (Robbins et al. 2011). Hypertension, chronic angiotensin II elevation, is considered a risk factor for

late AMD. Angiotensin II, a vasoconstrictor that regulates blood pressure and sodium retention, is of particular importance in this regard. It acts as a chemoattractant for classical splenic monocytes, worsening inflammation and CNV, and thus contributing to AMD (Roubeix et al. 2024).

4.2.3 Macrophages

Macrophages in the choroid could be derived from both mononuclear phagocytes and infiltrating monocytes. Similarly to microglia, macrophages differentiate into classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages are generally pro-inflammatory, and they are driven by Th1 cytokines, such as IFN-γ and TNF-α. Conversely, M2 macrophages facilitate tissue repair and neovascularization, and they are driven by Th2 cytokines, such as IL-4, IL-5, and IL-13 (Yang et al. 2016). M2 macrophages produce pro-fibrotic growth factors such as TGF-β and PDGF and activate fibroblasts and repair the tissue. On the contrary, M1 macrophages are able to facilitate the opposite effect, the ECM degradation. The reversal of fibrosis is done by releasing matrix metalloproteinases. This could potentially explain the limited efficacy of treatments for subretinal fibrosis (Dabouz et al. 2024; *Murakami et al. 2020).

When classical monocytes enter the eye, they differentiate into $CD11c^+$ macrophages, which have a pro-angiogenic role in nAMD by expressing high levels of VEGFA and CXCR4 (O'Koren et al. 2019; Droho et al. 2023b). It was shown that depleting $CD11c^+$ macrophages reduces CNV progression, indicating their role in disease pathogenesis (Droho et al. 2023a). Similarly, studies in mice with depleted CCR2, a receptor that acts as a chemoattractant for macrophages, have shown that these mice have smaller CNV lesions compared to control groups (Droho et al. 2023b). In the early stages of AMD, choroidal $CD68^+$ $iNOS^+$ macrophages, associated with classical activation (M1 phenotype), tend to be more closely located to the BM, suggesting an activated macrophage responding to changes in the subretinal space. Furthermore, the density of macrophages increased in submacular regions of the choroid compared to non-macular areas, indicating their active involvement in disease progression (*Wang et al. 2023).

Macrophage activation can be suppressed by α-MSH and calcitonin gene-related peptide, which help regulate inflammatory responses (Benque et al. 2018). In AMD patients, elevated intraocular levels of CCL2, IL-8, and VEGF act as chemoattractants for macrophages. Once recruited, circulating macrophages undergo M2 polarization, which enhances pro-angiogenic signaling and exacerbates CNV (*Murakami et al. 2020). Surprisingly, Apte et al. suggested that $CD11b^+$ cells may also have a suppressive role in new vessel formation (Apte et al., 2006). M1-like macrophages appear to reduce CNV, whereas M2-like macrophages promote it. The M2-associated cytokine IL-10, IL-4, and IL-13 has been implicated in CNV formation during aging (see Figure 5) (Zandi et al. 2015).

It was shown that succinate, a tricarboxylic acid cycle intermediate, plays a crucial role in mitochondrial ATP production, regulates macrophage polarization, and enhances the proliferation and migration of endothelial cells, worsening CNV. Succinate acts as a metabolic signal for local stress and

triggers pro-inflammatory signaling, resulting in M2 polarization and CNV progression. Furthermore, succinate increases retinol binding protein 4 secretion by macrophages, which activates VEGFR2 and enhances tip cell formation, cells at the tips of vascular sprouts (Shen et al. 2023). Melatonin may mediate the conversion of M1 to M2 macrophages, promoting tissue repair by Treg infiltration (Xu et al. 2020).

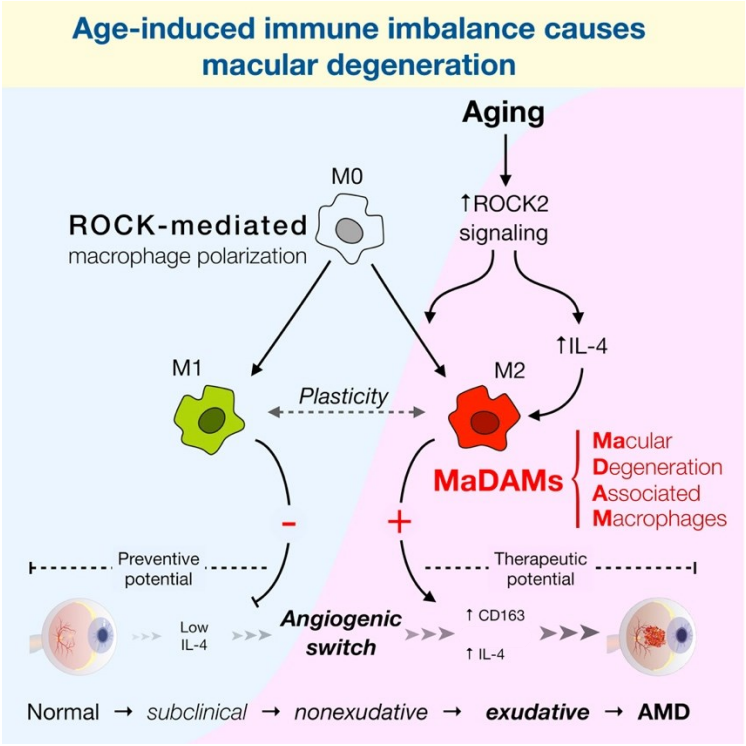

Figure 5: Rho-associated kinase (ROCK) determines macrophage polarization. Aging promotes M2 macrophage polarization, which is associated with CNV. Elevated IL-4 levels, which contribute to this polarization, and CD163, a marker of M2 macrophages, were observed (adapted from Zandi et al. 2015, with modifications).

4.2.4 Mast cells

Mast cells are a type of immune cell typically associated with asthma, allergies, anaphylaxis, and responses to parasites. These cells secrete a variety of mediators, such as neurotransmitters, cytokines, and chemokines, which play roles in immunomodulation, tissue repair, and angiogenesis. Although mast cells are absent from the retina, they are found in the choroid (McMenamin, Polla 2013; Dabouz et al. 2024). Research by Bhutto et al. has shown that the number of mast cells in the human choroid significantly increases in early AMD, and their numbers are particularly elevated in areas of exudative AMD and geographic atrophy. This suggests that mast cells may contribute to both the pathogenesis and remodeling processes involved in AMD progression (Bhutto et al. 2016).

Activated mast cells can influence choroidal function by increasing vasodilatation and vascular permeability (Bousquet et al. 2015). In addition to these effects, they induce angiogenesis and are consistently observed around the BM in both the early and late stages of CNV (Bhutto et al. 2016). These

cells further promote vascular remodeling by facilitating the migration of choroidal endothelial cells and vessel sprouting. Interestingly, mast cells have also been found to contribute to resistance against treatments based on VEGF by secreting matrix-degrading granzyme B. Increased levels of granzyme B observed in AMD patients are linked to increased blood vessel growth (Obasanmi et al. 2024). Levels of mast cell proteases, particularly tryptase, are augmented in patients with high-risk genetic predisposition. Suppression of mast cell activity could be a possible therapeutic option to prevent pathological neovascularization (Dabouz et al. 2024).

During angiogenesis, endothelial cells need to migrate across the ECM and the basement membrane. Mast cells mediate this process by tissue remodeling, including ECM composition, through their proteolytic enzymes or by activating ECM-degrading enzymes such as matrix metalloproteinases. ECM stores growth factors like VEGF or FGF. When the ECM is degraded, these stored growth factors are released into the surrounding environment, where they can promote angiogenesis (Dabouz et al. 2024).

4.2.5 T cells

Not only the innate immune system but also the adaptive immune system is involved in AMD pathogenesis. T cells, as part of the adaptive immune system, are characterized by developing long-term defense memory in response to pathogenic antigens. Furthermore, they can either amplify or suppress inflammation through the release of cytokines and interactions with other cells (Conedera et al. 2023; (Stürzbecher et al. 2025).

Tregs maintain immune balance by controlling inflammation and supporting tissue repair. In a healthy retina, the presence of Tregs is very low. However, during acute retinal inflammation, Tregs help limit excessive immune responses. IL-2 overexpression stimulates local Treg expansion, which reverses age-related retinal degeneration markers, such as gliosis or inflammation. Treg elimination results in increased glial reactivity, Müller cell hypertrophy, and an accumulation of phagocytes in the subretinal space. The adoptive transfer of Tregs from young mice was shown to partially reverse aged mice from retinal neurodegeneration. While Tregs from aged mice can also limit the pathogenicity of AMD, young Tregs show more efficacy and restore retinal homeostasis, preventing photoreceptor loss or gliosis (Llorián-Salvador et al. 2024; Lemaitre et al. 2023).

T helper $CD4^+$ cells (Th) and cytotoxic $CD8^+$ T cells (Tc) were found in the retinal parenchyma in response to retinal injury in mice. Similarly, in human cases, T cells were detected in both the macula and peripheral retina under pathological conditions (Conedera et al. 2023). $CD8^+$ T cells promote microglial activation, reinforcing a pro-inflammatory environment (Mohebiany et al. 2020). These cells also contribute to tissue damage through their cytolytic function, inducing cell death by disrupting target cell membranes with granules loaded with perforin-1 (Prf1). Selective elimination of $CD8^+$ T cells not only minimized retinal injury but also accelerated BRB recovery. The treatment with anti-$CD8^+$ antibodies

showed improved retinal function after the injury in mice. Similar results to $CD8^+$ T cell depletion were seen in mice lacking Prf1 (Conedera et al. 2023).

4.3 The complement system

The activation of the complement system plays a key role in the etiology of AMD. The complement system is an integral part of the innate immune response that helps antibodies to destroy pathogens. This inflammation-promoting system can be triggered by three major pathways: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway. Each pathway has a different trigger mechanism. However, this system all converges at the step of C3 cleavage (Schäfer et al. 2017).

Retinal microglia and RPE cells are the primary sources of complement components in the eye. As individuals age, there is a slight increase in the expression of complement genes in the retina, RPE, and choroid, helping to maintain retinal health. Genetic variations, such as single nucleotide polymorphisms in the alternative complement pathway, have been linked to an elevated risk of AMD development, suggesting that dysregulation of this system plays a role in disease susceptibility (*Wang et al. 2023).

CFH is essential for the regulation of inflammation. This protein switches C3b to its inactive form, C3bi, and weakens the active complex that forms between C3b and factor B. Normally, C-reactive protein (CRP) and glycosaminoglycans improve CFH functioning. However, the mutation in CFH (Y402H) reduces the affinity of CFH to CRP and alters the ability of factor H to recognize specific glycosaminoglycans. This can result in uncontrolled activation of the alternative pathway. High levels of unbound CRP can indicate chronic inflammation and are considered a risk for AMD (*Bhutto, Lutty, 2012).

4.4 The role of cytokine production

Cytokines are small proteins secreted by cells that play a key role in regulating intercellular communication. Macrophages, microglia, Müller cells, and endothelial cells are the main sources of cytokines in the retina (*Barnes, Somerville, 2020).

4.4.1 Anti-inflammatory cytokines

To maintain the immune-privileged state of the eye, cytokines such as TGF-β and IL-10 are secreted to promote anti-inflammatory responses, which prevent excessive inflammation and promote ocular immune privilege (Chang et al. 2023). RPE cells produce both pro-inflammatory and anti-inflammatory cytokines. Notably, RPE cells secrete a large amount of anti-inflammatory cytokines, especially IL-10, which suppresses the production of pro-inflammatory cytokines and inhibits the proliferation of antigen-specific T cells (Idelson et al. 2018; Hansen et al. 2019).

4.4.2 Pro-inflammatory cytokines

Under pathological conditions, cytokine levels can change. Müller cells, for instance, are a major source of cytokines, including IL-33, which regulates inflammation and photoreceptor degeneration

following retinal stress. IL-33 production and the population of IL-33$^+$ Müller cells are elevated in advanced AMD, promoting CCL2 expression and the CCR2$^+$ myeloid cell accumulation in the photoreceptor layer of the retina. However, IL-33 also supports mitochondrial metabolism, and its loss can result in susceptibility of the RPE to oxidative stress, a condition that favors AMD development, due to its reliance on glycolysis. The data show that the RPE of AMD patients has decreased IL-33 levels compared to normal age-matched donors, highlighting the increased oxidative stress in the diseased retina (Xi et al. 2016).

RPE cells secrete IL-1α, promoting inflammation, angiogenesis, and NLR family pyrin domain containing 3 (NLRP3) inflammasome activation in AMD (Bhattarai et al. 2022). TNF-α and IL-1β contribute to disease progression by disrupting the BRB (Kim et al. 2025). IL-1β also induces VEGF, promoting CNV, while TNF-α exacerbates AMD by upregulating VEGF and disrupting barrier function (Sun et al. 2024).

In AMD patients, the at-risk CFH Y402H polymorphism is linked to elevated pro-inflammatory cytokines, including IL-6, IL-18, and TNF-α, which correlate with disease progression and geographic atrophy. IL-6 and TNF-α contribute to CNV, while prolonged TNF-α and IL-18 exposure cause RPE cell damage and atrophy (Cao et al. 2013). Additionally, TNF-α, IL-6, and IL-1β disrupt RPE tight junctions by activating the transcription factor nuclear factor kappa B (NF-κB), which results in reduced zonula occludens-1 expression, increased BRB permeability, and enhanced inflammation. The breakdown of BRB allows infiltration of immune cells and the accumulation of pro-inflammatory mediators, exacerbating AMD pathology. When the RPE is compromised, ACAID no longer functions properly, leading to loss of immune privilege and retinal pathology (*Zhu, Hong, Zhou, 2023).

IL-17A contributes to the activation of mitogen-activated protein kinase and NF-κB signaling pathways, which induce immune cell recruitment. This cytokine is primarily produced by Th17 cells, and in the healthy retina, the inflammation driven by IL-17A is balanced by Treg cells and anti-inflammatory cytokines to prevent excessive inflammation. While IL-17A deficiency was thought to reduce CNV, recent findings suggest that this cytokine protects against retinal damage by upregulating heme oxygenase-1, which prevents oxidative stress and apoptosis (Chang et al. 2023).

4.2.3 Chemokines

Chemokines, which are signaling molecules that mediate the recruitment of immune cells to sites of inflammation, are often upregulated in retinal diseases like AMD (Choi et al. 2022). For instance, CCL2, along with other chemokines like C-X-C motif ligand (CXCL) 1 and CXCL10, show elevated expression in the retina during AMD progression. CCR2, a receptor for CCL2, is specifically expressed on choroidal neovascular endothelial cells in AMD and is considered a potential therapeutic target for managing CNV in AMD (Falk et al. 2014; Sennlaub et al. 2012; 2013)

5 A future perspective on the treatment of AMD

Current treatments for AMD are primarily focused on managing inflammation and vascular abnormalities. However, a future perspective on the treatment of AMD is increasingly focused on the role of immune cells in inhibiting disease progression. Targeting immune pathways by regulating immune cell activity, restoring the BRB, and refining complement system interventions could offer new opportunities for therapeutic approaches.

In this context, the regulation of the complement system is gaining attention. Several therapeutics targeting complement factors like C3 or C5 are being evaluated in clinical trials as a potential treatment for AMD. These therapeutics can be delivered by gene therapy using adeno-associated virus vectors (*Armento, Ueffing, Clark, 2021). Similarly, modulation of cytokine levels is a potential treatment option for AMD, with compounds such as polyethylene glycol-coated rhodium nanozyme inhibiting TNF-α and IL-1β, which are cytokines that contribute to the retinal inflammation (Sun et al. 2024). In addition, other potential therapeutic approaches, including the use of tyrosine kinase inhibitors, gene therapies (Ahmed et al. 2023), and P2X7 receptor antagonists, have been proposed as a potential therapeutic strategy to mitigate this effect (Cao et al. 2023).

The M1 to M2 polarization of microglia and macrophages presents a complex but promising therapeutic target. Microglia polarization suggests that promoting anti-inflammatory M2 polarization could help alleviate inflammation. For example, Asiatic acid has been shown to attenuate pro-inflammatory signaling and promote M2 polarization (Fang et al. 2021). Conversely, macrophage polarization proposes that M2 polarization results in CNV. It was shown that a selective Rho-associated kinase 2 inhibitor reduced M2-like macrophages, suppressed angiogenesis, and upregulated M1 macrophages without affecting macrophage recruitment (Zandi et al. 2015). Targeting macrophage metabolic pathways, such as succinate metabolism, has been shown to prevent M2 polarization and reduce CNV severity (Shen et al. 2023). Additionally, suppressing microglial activation by inhibition of colony-stimulating factor-1 receptor in the ischemic eye has been proposed as a potential strategy to delay retinal degeneration and enhance retinal ganglion cell survival (Jovanovic et al. 2019)

Inhibition of protein kinase C or regulating junctional adhesion molecule C activity could help prevent BRB dysfunction and maintain homeostasis (Hou et al. 2021). Additionally, some research suggests that targeting splenic monocyte recruitment may slow photoreceptor degeneration. Monocytes originating from the spleen differ functionally from bone marrow-derived monocytes, exhibiting increased resistance to elimination within inflamed tissues. In this regard, ATR1 blockers, such as Iosartan, have been shown to be effective in reducing monocyte infiltration (Roubeix et al. 2024). Furthermore, therapies targeting the NLRP3 inflammasome and its associated pathways, including the use of anti-retroviral drugs and TLR antagonists, are being explored to suppress inflammation and reduce cell death in the retina (*Brandli, Vessey, Fletcher, 2024; Sekar et al. 2023). Fingolimod, a sphingosine-1-phosphate antagonist, has shown

protective effects by modulating peripheral leukocyte migration and reducing vascular permeability (Sorenson et al. 2022).

Treg-based therapies may help prevent AMD progression . Depleting $CD8^+$ T cells enhances recovery and reduces damage in AMD models, suggesting $CD8^+$ T cell targeting as a potential treatment. Prf1-lacking mice showed a similar result to $CD8^+$ depletion. Preclinical studies have shown that Prf1 inhibitors prevent early retinal degeneration

(Llorián-Salvador et al. 2024)

6 Conclusion

AMD is a complex disease in which immune dysregulation represents a key component of the (Fleckenstein et al. 2021) underlying pathogenesis. This thesis has explored immunocompetent cells, including microglia, macrophages, mast cells, monocytes, and T cells, in the pathological transformation of the retina from an immune-privileged to a chronic inflammatory state. The work has also addressed how cytokine imbalance, complement system dysfunction, and immunocompetent cell signaling interact to amplify the effect and further contribute to the development of AMD.

Current therapies for AMD are insufficient to completely cure the disease, highlighting the need for further research into the immunopathological mechanisms. In a dysregulated immune response in the retina, microglia become chronically activated and polarize into two phenotypes, with the pro-inflammatory M1 phenotype predominating over the anti-inflammatory M2 phenotype. Similarly, macrophages polarize into M1 and M2 phenotypes, however, studies have shown that M2 macrophages promote angiogenesis, whereas M1-like macrophages reduce CNV. The role of macrophages in promoting or resolving fibrosis may help explain the limited efficacy of treatments for subretinal fibrosis in wet AMD. Several studies have identified small molecules, such as succinate and melatonin, as modulators of M2 macrophage polarization. In addition to macrophages, monocytes infiltrate the retina when the BRB is compromised. Splenic monocytes have been shown to drive inflammation and CNV in AMD. CCR2 deficiency has been associated with reduced CNV severity, suggesting the role of NR4A1, the transcription factor necessary for the maturation of non-classical monocytes, in the disease progression. Moreover, Tregs help maintain immune balance during acute retinal inflammation by limiting excessive immune responses through cytokine expression. Additionally, it was shown that the transfer of young Tregs partially reversed retinal neurodegeneration. On the contrary, Th and Tc cells promote microglial activation and contribute to tissue damage. Inhibiting these cells, particularly Tc cells, could offer a potential therapeutic strategy. Mast cells further contribute to disease progression through angiogenesis, increased vasodilatation, and vascular permeability. Finally, dysregulation of the complement system is linked to an elevated risk of AMD development, with CFH being a key regulatory component.

The findings demonstrate that inducing polarization to a certain phenotype or inhibiting immune cells and small molecules through several kinds of mechanisms could potentially offer a prospective

therapeutic option in the future. However, the complex nature of the disease and the interconnection of immunocompetent cells further complicate the understanding of this condition.

AMD is a combination of immune, vascular, and metabolic dysfunctions. Current research directions in AMD are focused on a deeper understanding of individual immune cell types and how they interact within the retinal environment. Although research gives a broader understanding of this disease, further studies are essential to translate these insights into effective and personalized therapeutic strategies.

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