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Age-related macular degeneration and changes in the extracellular matrix

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Age-related macular degeneration (AMD) is the leading cause of permanent, irreversible, central blindness (scotoma in the central visual field that makes reading and writing impossible, stereoscopic vision, recognition of colors and details) in patients over the age of 50 years in European and North America countries, and an important role is attributed to disorders in the regulation of the extracellular matrix (ECM). The main aim of this article is to present the crucial processes that occur on the level of Bruch's membrane, with special consideration of the metalloproteinase substrates, metalloproteinase, and tissue inhibitor of metalloproteinase (TIMP).
A comprehensive review of the literature was performed through MEDLINE and PubMed searches, covering the years 2005–2012, using the following keywords: AMD, extracellular matrix, metalloproteinases, tissue inhibitors of metalloproteinases, Bruch's membrane, collagen, elastin.
In the pathogenesis of AMD, a significant role is played by collagen type I and type IV; elastin; fibulin-3, -5, and -6; matrix metalloproteinase (MMP)-2, MMP-9, MMP-14, and MMP-1; and TIMP-3. Other important mechanisms include: ARMS2 and HTR1 proteins, the complement system, the urokinase plasminogen activator system, and pro-renin receptor activation.
Continuous rebuilding of the extracellular matrix occurs in both early and advanced AMD, simultaneously with the dysfunction of retinal pigment epithelium (RPE) cells and endothelial cells. The pathological degradation or accumulation of ECM structural components are caused by impairment or hyperactivity of specific MMPs/TIMPs complexes, and is also endangered by the influence of other mechanisms connected with both genetic and environmental factors.

Keywords: **AMD • Extracellular Matrix • Metalloproteinases • Tissue Inhibitors of Metalloproteinases • Collagen • Bruch's Membrane • Elastin**

Abbreviations: **AMD** – age-related macular degeneration; **ARMS2** – age-related maculopathy susceptibility 2; **BLamD** – basal laminar deposits; **BLinD** – basal linear deposits; **BM** – basic membrane; **BrM** – Bruch's membrane; **CEP** – carboxyethylpyrrole; **CNV** – choroidal neovascularization; **DHA** – docosahexaenoic acid; **ECM** – extracellular matrix; **GA** – geographic atrophy; **HTRA1** – high temperature requirement factor A-1; **MAC** – membrane attack complex; **MMP** – matrix metalloproteinase; **MT-MMP** – membrane-type metalloproteinase; **PRR** – pro-renin receptor; **RPE** – retinal pigment epithelium; **SD** – soft drusen; **TIMP** – tissue inhibitor of metalloproteinases; **uPAR/uPA** – urokinase plasminogen activator receptor/urokinase plasminogen activator; **VEGF** – vascular endothelial growth factor

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Bacground

The extracellular matrix (ECM) is composed of stromal substance (stroma) and basement membranes that are stretched along the border between this matrix and the tissues, that is, between the epithelium and the endothelium. The ECM represents a supportive frame for the cells (tissues and organs) and creates the internal environment for nutrient transport, product metabolism, and signal conduction (for proper functioning and protection against outer undesirable factors). The ECM also takes part in regulating the physiological processes of differentiation, proliferation, migration, and cell adhesion [1–4]. The physiological balance between synthesis and disintegration of the ECM components allows for both creation and maintenance of proper tissue architecture. The key role in the continuous rebuilding of connective tissue, both physiological and pathological (processes of growth and reconstruction), is played by endopeptidases, also called metalloproteinases, or matrix metalloproteinases (MMPs), which are able to degrade all of the structural elements of the ECM: basement membranes, cytokines, growth factors, chemokines, and receptors on the cell membranes [1–6]. MMPs are synthesized and secreted as latent enzymes; they become active in the presence of zinc and calcium ions and act on the surface of the cell or in the area around it. MMPs can be divided into several types on the basis of the decomposition of substrates: collagenases, gelatinases, stromelysin, elastase, and membrane metalloproteinase [1–3,5]. The production and secretion of metalloproteinases is controlled genetically [1–3,5]. The activity of MMPs is strictly regulated by tissue-inhibitor metalloproteinases (TIMPs), with the 4-endogenic TIMPs comprising TIMP-1, -2, -3, and -4 [1–3,5,6]. MMP/TIMP complexes are responsible for regulating the cascade of enzymatic reactions occurring in embryogenesis, morphogenesis, cell apoptosis, inflammatory reaction, angiogenesis, and other processes [1–8].

Disorders of regulation of the substrate complex/MMPs/TIMPs (impairment or hyperactivity) leads to general pathological conditions such as rheumatoid arthritis, heart diseases, blood vessel diseases, atherosclerosis, ulcers, multiple sclerosis, metastasis, and autoimmune diseases [1–3,5,7,8], as well as eye diseases such as retinal dystrophy [9–11], age-related macular degeneration (AMD) [12–17], pseudoexfoliation syndrome [18–20], fibrosis of the lenticular capsule after phacoemulsification treatment [21–25], diabetic retinopathy [26,27], proliferative diabetic vitreoretinopathy [16], and epiretinal membrane of proliferative diabetic retinopathy [28].

AMD can be caused by many factors, but advanced age and its related physiological cell apoptosis and tissue involution, together with genetic predisposition, are the strongest risk factors [9,12,14,29–34]. Other important factors include sex [35], environmental influences such as smoking cigarettes [36], heart and vascular disorders, hypertension, dyslipidemia/hypercholesterolemia, diabetes, obesity, improper diet, and sedentary lifestyle [37–42]. The pathological area involved in AMD is represented by photoreceptors, the retinal pigment epithelium (RPE), ECM (Bruch's membrane [BrM]), and the choriocapillaris [12,17,33]. The pathological features of AMD are triggered by the deregulation of metabolic processes on the level of RPE cells; however, the area of disorders lies within the ECM [12–14,29,43–45].

The most significant symptom of early AMD is the presence of inflammatory deposits, the soft drusen that appear in the area of the BrM, but which are larger than 125 µm and confluent; these in turn represent an important risk factor for further development of AMD [44,46–48]. Most patients with advanced AMD have dry AMD in the form of geographical atrophy of the central retina covering the photoreceptors/RPE cells/BrM/choriocapillaris complex [14]. About 10–15% of all patients with advanced AMD have the wet, or neovascular, form (choroidal neovascularization, CNV) [14], which occurs in 4% of patients who are over 75 years old [34]. As a result of pathological angiogenesis, the vessels from the choroid appear to proliferate – after crossing the ECM border, they penetrate under the retina and their immaturity and the leakiness of their vascular walls causes multiple leaks of serum and lipoproteins to occur, as well as numerous hemorrhages [8,14,49,50]. The overall process finally results in scarring and irreversible loss of central vision.

Molecular Character of Changes in the ECM in AMD

The 2–4 µm-thick BrM [17] is the ECM and acts as a frame for the metabolically active RPE cells, as well as a physical barrier for their passage and that of the endothelial vessels; moreover, it regulates the diffusion of nutrient molecules between the retina and the choroid [17,51–53]. The BrM is composed of 2 basement membranes – 1 for the RPE cells and 1 for the endothelium of the choriocapillaris – which are rich in collagen type IV (non-fibrillar), fibronectin, and laminin. Between the basement membranes are 2 layers (inner and outer) of structural collagen, composed of collagen type I and type III (fibrillar). Both of the collagen layers embrace the middle layer of the BrM, like a sandwich built mainly of elastin [14,15] (Figure 1).

RPE cells control the synthesis of all the structural elements of the BrM, mainly the most abundant proteins – collagen type I, collagen type IV, and laminin (which is not a collagen) – as well as the metalloproteinases and their tissue inhibitors [54]. The synthesis of metalloproteinases undergoes complex regulation

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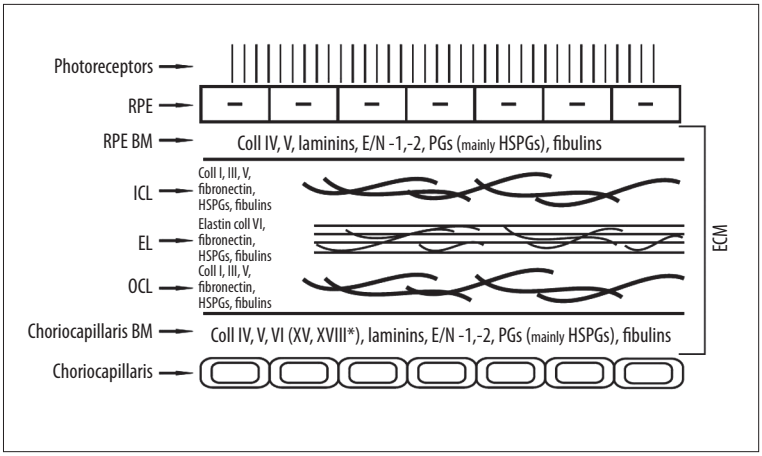

Figure 1. The composition of regular human extracellular matrix (Bruch's membrane). E/N – entactin/nidogen, PGs – proteoglycans, HSPGs – heparan sulphate proteoglycans.

by growth factors, cytokines, endothelins, interleukins, prostaglandins, and growth hormones [1,55]. There are 2 forms of secreted metalloproteinases: free or anchored in the cell membrane (membrane-type metalloproteinases; MT-MMPs) [1–3,5]. The role of MMPs is not limited to the degradation of the BrM; growth factors are secreted from cell membranes that increase the accessibility of MMPs and strengthen their activity [1–3,5]. Increased activity of MMPs stimulates the secretion of TIMPs, which bind to inactive pro-MMPs or active metalloproteinases. TIMP-1 inhibits the activity of MT-MMPs; TIMP-2 and -3 can bind to all types of MMPs; and TIMP-4 inhibits MMP-1, -2, -3, -7, and -9 [2,5,56] (Table 1).

The elastic layer of the BrM plays a key role in the pathogenesis of advanced neovascular AMD [87,88]. With increasing age, the number of basophilous fibers increases, which in turn leads to calcification and synchronously to the loss of elasticity of the BrM [14]; the developing destruction of the elastic fibres releases proteins, which are strong pro-angiogenic factors [89,104]. Regardless of an individual's age, the elastic layer is 3 to 6 times thinner and 5 times more porous in the area of the macula than it is on the rim of the retina [87]. The thinner and more porous elastic layer causes the BrM to become a weaker frame for the RPE cells and may trigger CNV development in this part of the retina [87,88]. Some researchers [87,105,106] suggest that the defects in the BrM are essential factors – whereas others [107] maintain that they are not – for the CNV to enter the area of the ECM of the macula. Elastin has strong structural and functional connections with fibulins [92–95] and enters into a reaction with the age-related maculopathy susceptibility 2 (ARMS2) protein (see below) [9]. Elastin is degraded by (metallo)elastase MMP-12, and gelatinase A (MMP-2) and B (MMP-9) [1,2,5,108,109]. Smoking cigarettes is thought to be a strong stimulator for the destruction of elastic fibers; this key modifiable environmental risk factor for the development of AMD also triggers auto-immunological processes against elastin [110,111].

Metalloproteinases of the ECM and Their Tissue Inhibitors are Important for the Pathogenesis of Both Dry and Wet AMD

In AMD, RPE cell dysfunction results in disorders in the activity of MMPs/TIMPs and their substrates. MMP-2 and MMP-9, being regulated by TIMP-2 and TIMP-1, respectively [2,5,8], play a key role in the pathogenesis of AMD [43,45,112,113] and in both early dry AMD [13,43,45] and advanced wet (neovascular) AMD [4]. MMP-2 and MMP-9 can digest the main structural elements of the ECM: collagen IV, collagen V, fibronectin, and laminin [1,2,5]. Loss of MMP-2 activity leads mainly to an increase in collagen IV, as well as to an accumulation of deposits under the RPE layer [114]. MMP-2 is the most abundant enzyme synthesized by RPE cells [43,45,113]. The disordered activity of MMP-2 is the main cause of early AMD development [13,43,45]. MMP-2 is secreted as an inactive pro-enzyme that is activated by MMP-14 near the pro-MMP-2/TIMP-2/MMP-14 complex [2,35,115]. The activation process takes place exclusively when the TIMP-2 level is low in relation to that of MMP-14 in this 3-element complex [2,115]. MMP-14 indirectly influences collagen by activating MMP-2, but also directly influences it by causing an increase in collagen I and III [35].

MMP-1 and TIMP-3 also have important roles in the development of AMD. MMP-1 degrades collagen I, II, III [1,2,5] and the decrease in its activity favors the development of soft drusen. In AMD-prone eyes (family history, influence of crucial environmental risk factors), the activation of MMP-1 by lysosomal enzymes in ageing and dysfunctional REP cells, together with the simultaneous effect of the MMP-9 and urokinase plasminogen activator receptor/urokinase plasminogen activator (uPAR/uPA) system (activated by interleukin-1), leads to the development of advanced neovascular AMD [15,116,117]. TIMP-3 strongly binds to glycosaminoglycans in basement membranes [44] and has a role in cell apoptosis [10,118,119]. RPE cells, when exposed to blue light (relative AMD risk factor), diminish TIMP-3 production, which consequently causes an increase in the

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Table 1. Structural elements of the ECM crucial in the development of early and/or advanced age-related macular degeneration: their characteristics, biological function, and digesting matrix metalloproteinases (MMPs).

Substrate	Localization/Biological Function	Substrate-digesting MMPs	Role in development
	Basement membranes (BMs)		
Collagen IV	Main, and most abundant element, of the BM RPE ($\alpha3\alpha4\alpha5$ molecule – is responsible for fluid/membrane barrier) and the endothelium ($\alpha1\alpha1\alpha2$ molecule) [57–63]. Stabilizes and integrates BM and takes part in the process of angiogenesis and haemostasis [59,61]. Despite its prevalence and abundance, it is not required for initiating the BM process [62]	-2, -9 [2,8]	SD/CNV [54,59,61]
Laminin(s) (12 isoforms) LAMA(α), LAMB(β), LAMC(γ)	"Big" non-collagen element of BM – proteoglycan [64–68]. Initiates and is necessary for the BM process [64,65,69,70] and binds to collagen directly or by means of entactin/nidogen – see below [59,71]. Supports the structural integrity of the BM and adhesion of the RPE and endothelium. Also mediates signal transmission by means of the following cell receptors: integrins, proteoglycans, and glycoproteins (e.g., dystroglycan) – see below [59]	-2, -9, -7, -19, MT1-MMP [2,5]	
Entactin/Nidogen 2 isoforms: (E/N-1, -2)	"Small" components of BM – proteoglycans [68]. Necessary for membrane formation and binding of laminin to collagen and fibulins – see below [59,72–74]. Responsible for adhesion by mediation of integrins or other receptors [59,75]	-3, -13 [2,5]	
Proteoglycans (PGs)	Chondroitin/dermatan sulphate and mainly heparan sulphate. With proteins of PGs, glycosaminoglycans create strong hydrophilic and water-absorbing gel-like structures, in which collagen fibres are drowned [76]. Support the histo-architecture, regulate adhesion and differentiation of cells and the activity of growth factors, and play a key role in selective ultrafiltration of the ECM [47,58,77–80]	-3, -10, -11 [2,5]	
	ICL, EL, OCL		
Collagen I	Main element of the ICL and OCL [59,81]. Renovation of fibres, adhesion of cells, interactions in the ECM [82-84]	-1, -2, -8, -9, -13, -18, MT-MMPs: -14, -15, -16, -24 [2,5,8]	SD/CNV [54,8,85,86]
Elastin	Main structural element of the EL. Influences the elasticity and endurance of the ECM [87-89]	-2, -9, -12 [2,8]	CNV [87,88]
Fibronectin	Proteoglycan. Shapes and degrades collagen [84] and facilitates adhesion of the RPE and the endothelium by binding integrins to collagen (see below) [58,76]. Also necessary for the formation of choroid vessels [85]	-2, -9, -7 [2,5,8]	
Fibulins (mainly-3, -5, -6)	"Small" components of the BM, ICL, EL, and OCL. Form, stabilize, and anchor elastic fibres to the BM by binding elastin and laminin to integrins [9,68,90–92] FBLN-3 inhibits the CNV by limiting secretion of MMP-2, -3, and -9 [92]		SD/*GA, *CNV [9,92–96]
Integrins 2 isoforms: (ITG-A, -B)	Next to dystroglycan, they are the main surface receptors of the RPE and endothelium for collagen, laminin, and fibronectin [97–102]. Polygonal network of laminin appears as a result of the binding of neighbouring cells, anchored to integrins or dystroglycans. The process is steered by cellular actin [103]		

BM – basement membrane; ICL – internal collagenous layer; EL – elastic layer; OCL – outer collagenous layer. * Familial.

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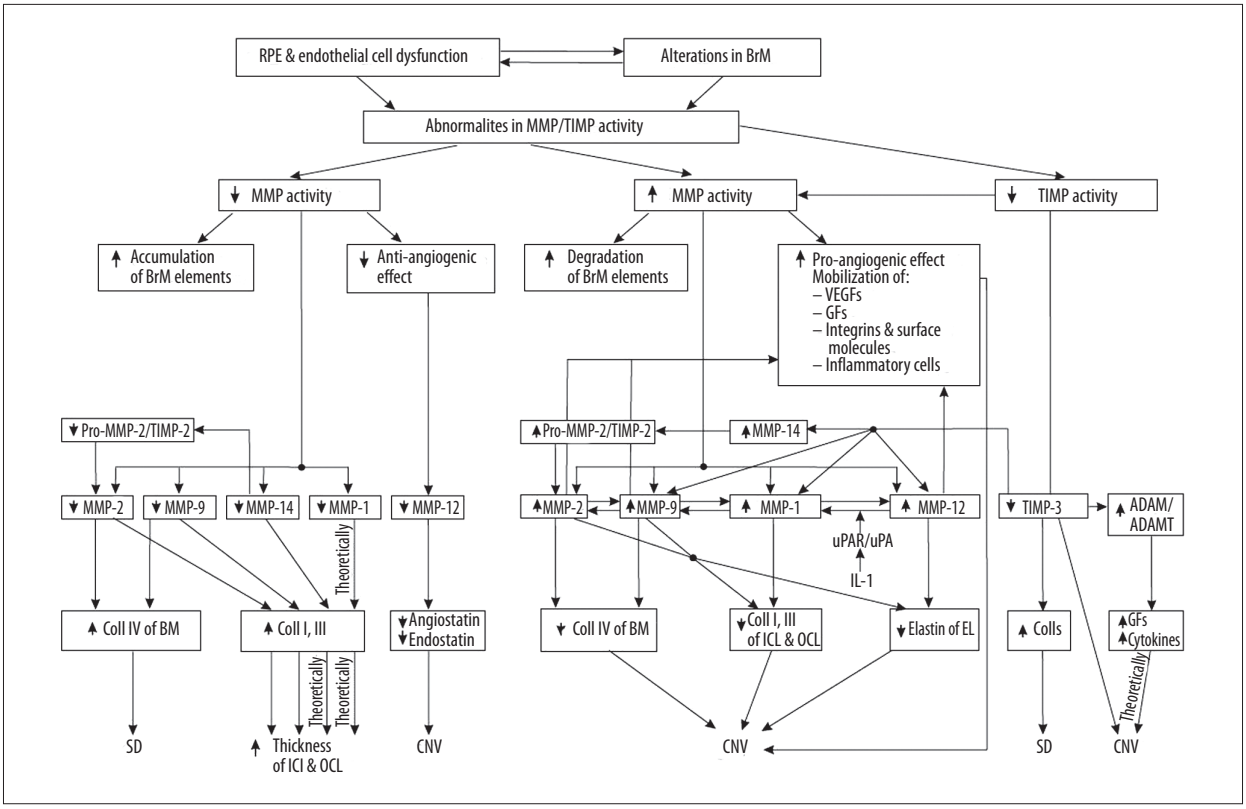

Figure 2. Matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) significant in the pathogenesis of early and late AMD. IL-1 – interleukin-1.

amounts of various collagens and in the development of early dry AMD [15,120]; on the other hand, TIMP-3 demonstrates a protective influence, since it inhibits the development of neovascularization [121] (Figure 2).

Histological and Clinical Aspects of Changes in the ECM and Other Mechanisms (Apart from MMP/TIMP Complexes) That Regulate the ECM in Both Early and Advanced AMD

As a result of RPE cell ageing and disorders in their functioning, the structure of the ECM changes [82]. The amount of collagen I [122], III, IV, and V increases [123], as does the amount of non-soluble collagen (responsible for facilitating the accumulation of metabolic waste and lipoproteins, growth factors, and cytokines [123]), and the network of collagen fibers in both collagen layers of the BrM becomes irregular [124]. An increase in glycosaminoglycans is partially responsible for the changes in the metabolism of collagen [78]. The elastic layer of the BrM loses its flexibility and becomes porous and fragile [125]. In addition, the amount of collagen increases, mainly in the internal collagenous layer [78,122,123]; basal laminar deposits (BLamD) [126–128] and drusen [126,128] are formed; and fats accumulate [129–131]. All of these factors cause a minimum triple thickness of the BrM [78,126,128], which worsens filtration to and from the retina [78,132]. The situation is further worsened by the decrease in blood flow caused by the diminishing vascular lumen and the amount of choriocapillaries [133–136] (Figure 3).

The symptoms of RPE and ECM change disorders in early AMD are crucial for the pathogenesis, invisible clinically, of early and advanced BLamD and basal linear deposits (BLinD) [125,137–139]. BLamD are stored and accumulated between the cytoplasmic and the basement membrane of RPE cells [125,137,140], whereas BLinD are stored and accumulated in the ECM between the RPE basement membrane and the internal collagen layer of the BrM [125,137,138]. BLamD comprise membrane proteins and fibrous long-spacing collagen, with cyclic repeatability of the collagen polymer every 100 to 120 nm [125,137], which react together with antibodies against elements of the basement membrane such as collagen type IV, proteoglycans, and laminin [125,137]. The early BLamD does not cause separation of the RPE cells from the internal collagen layer of the BrM, but accumulated, advanced, and thick BLamD can cause the separation of the RPE from the ECM. This separation, together with the decrease in permeability of the BrM (which becomes thicker and hydrophobic), simultaneous with the worsened blood supply caused by the choroid's capillary vessels, worsens the

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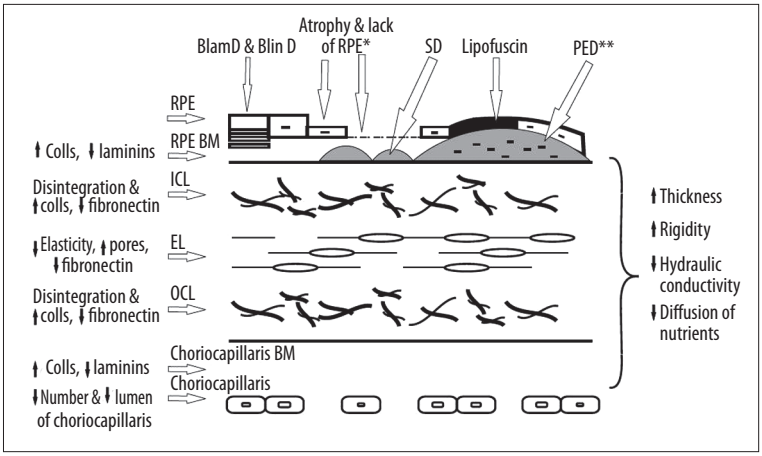

Figure 3. Pathological changes in the retinal pigment epithelium, extracellular matrix, and choroid in age-related macular degeneration. PED - pigment epithelial detachment. * Programmed cell death – apoptosis; ** cell death caused by separation from its BMs – anoikis [14].

metabolism of the RPE cells, affecting the ability of these cells to supply the photoreceptors [141–144]. Both BLamD and BlinD are an index of the degree of degeneration of photoreceptors and RPE cells, which correlates positively with a decrease in visual acuity and clinically visible pigment changes in the macula [125,139,140]. The deposits in question also influence the development of advanced forms of AMD [139]. The accumulated basal deposits may trigger disorders caused by changes in the ECM and deepen the process of lipofuscinogenesis, an accumulation of lipofuscin that takes place in the RPE; ie, age pigment, which develops from fully or partially digested outer segments of photoreceptors as a result of the gradual failure of liposomal enzymes in the RPE [145–147]. In the basal deposits, present in patients with neovascular AMD, 2 new forms of collagen aggregates, from untypical collagen polymerization, have been reported. The first form appears as parallel stripe-shaped structures, singly and/or in clusters, and is stretched from the internal surface of BLamD to the ECM; this form is morphologically similar to the collagen of the short-chained type. The second form appears as aggregates, similar to long-fiber collagen, and is periodically separated with characteristic dense strands [148]. According to the authors, the leakage of various factors from the neovascularization that trespasses into the area of the BrM and from the basal deposit may both induce physico-chemical changes in the ECM, which in turn may trigger untypical polymerization of the collagen molecules into aggregates similar to the stripes and long fibers of collagen [148]. Deposition of these new structures increases the BLamD thickness to a high degree and simultaneously worsens the nutrient and oxygen supply of the RPE/photoreceptors, which in turn maintains neovascularization [148].

The basal deposits, with diameters of over 25–30 μm, turn into clinically visible soft drusen, which are conducive to serous separation of the RPE from the ECM [9,139,149–151]. They are a risk factor for developing advanced forms of AMD during the next 5 to 10 years [152,153]; i.e., the geographical atrophy or neovascular form of AMD [139,154–157]. Eyes without drusen and with only the pigment changes (resulting from the elimination from the ECM of the RPE cells, which are loaded with lipofuscin and have lost their microvilli and ability to adhere to the ECM) [141–144,158], show a slower AMD process and have a lower risk of developing the advanced form of AMD during the next 5 to 10 years [152,153]. Drusogenesis takes place and lasts in the ECM for many years. It is a complex and multifactorial process, as evident from the composition of drusen: phospholipids, glycolipids, saturated and unsaturated fatty acids, cholesterol, approximately 130 various kinds of proteins, carbohydrates, fibronectin, ubiquitin, vitronectin, integrins, apolipoproteins, and immunoglobulins. Drusen also contains components of the complement complex, including, among others, the membrane attack complex (MAC), adducts of the carboxyethylpyrrole (CEP) protein (see below), MMPs, TIMPs, and others [14,114,149,159–162]. Drusogenesis is a side effect of both dysfunction and degeneration of RPE cells; however, it may also indicate a chronic para-inflammatory (which in some aspects is similar to inflammation, but not classic inflammation) and immunological condition in the ECM [163–169]. The phagocytes (leukocytes, lymphocytes, and macrophages) and complement system attempt to clear the ECM of the accumulated metabolic waste of the RPE [170–172].

The classic and alternative pathways of the complement system (which does not require the presence of a typical pathogen), activated by factors that are dependent on and independent from lipofuscinogenesis (an oxidized albuminous element of lipofuscin, bis-retinoid pyrimidine A2E, is one of the strongest cytotoxic stimulants of the alternative pathway, and is only exceeded by CEP and isolevuglandin), lead to the creation of the MAC and the destruction (lysis) of the aggressor's cells after the spontaneous hydrolysis of the C3 factor (classic pathway) or the C3b factor (alternative pathway) [170,172–177]. The complement system is an integral element of the inborn (not specific) immunological response, and it supports phagocytosis and controls the inflammatory reaction process [170,172]. However, in conditions of insufficient control in the AMD, the

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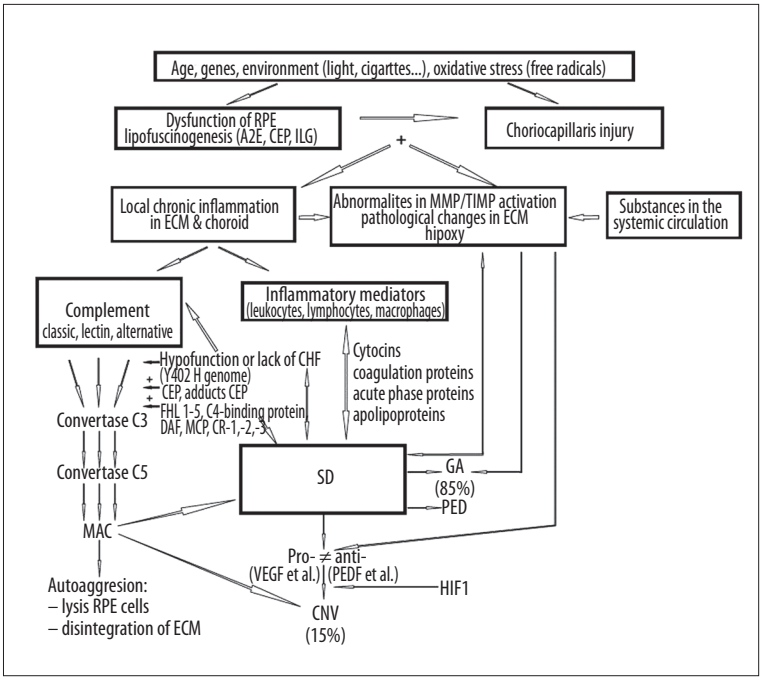

Figure 4. Schematic presentation of the mechanisms causing early and advanced forms of age-related macular degeneration.
A2E – bis-retinoid pyrimidine,
CEP – carboxyethylpyrrole protein,
ILG – isolevuglandin,
CFH – complement factor H,
FHL – family of factor H-like proteins,
DAF – membrane decay-accelerating factor, MCP – membrane cofactor protein, CR – complement receptor,
MAC – membrane attack complex,
GA – geographical atrophy,
PED – pigment epithelium detachment,
VEGF – vascular endothelial growth factor, PEDF – pigment epithelium-derived factor, HIF-1 – hypoxia-inducible factor-1.

complement system starts to attack both the drusen material and its own RPE cells, especially in patients with the Y402H gene polymorphism, which causes hypofunction or lack of the protective complement factor H, which in turn slows down the cascade of reactions connected with an increase in MAC, especially within the range of the alternative pathway. This leads to deep disintegration of the ECM [178–181]. Apart from complement factor H, other serum (plasmatic) suppressors of the activity of the complement system are important, including the family of factor H-like proteins 1–5, C4-binding proteins, and surface protein such as membrane decay-accelerating factor CD55, membrane cofactor protein CD46, and receptors of the complement system CR1, CR2, and CR3 [177,182]. In the mobilization of the immune system and the auto-aggressive response regarding RPE cells and the ECM, a pivotal role is also played by the CEP protein and its adducts, which are generated in blood as a result of CEP conjugation with circulating proteins such as plasma albumin [149,183]. CEP is a derivative of the free-radical oxidation of phospholipid docosahexaenoic acid (DHA), which is the main representative of polyunsaturated fatty acids, which are abundant in plasmatic membranes of photoreceptors digested by the RPE cells [183,184]. DHA is especially prone to the oxidation process, which is also favored by relatively high oxygen partial pressure in the central part of the retina [184–186]. Oxidized DHA-CEP products and CEP adducts are present in the lipofuscin of RPE cells, the drusen of the ECM, and systemic circulation [149,183]. They are strongly immunogenic, and therefore constitute a target for the immune system and stimulate the production of anti-CEP antibodies and anti-CEP auto-antibodies (because the adducts are endogenic compounds with antigen features) [149,183]. CEP adducts caused the development of human AMD (drusen, geographical RPE atrophy, neovascularization) in immunized animals [187, 188]. They also stimulate angiogenesis independently from vascular endothelial growth factor (VEGF; see below) [189]. In the neovascular type of AMD, the ECM is affected by the influence of the pro-angiogenic forces (generated by the RPE) on the choroid and therefore becomes the area of neovascularization invasion. Hypoxia, but also hyperactivity of the complement system, together with the inflammatory process, leads to disturbances in the pro/anti-angiogenic balance. The increased RPE expression of the angiogenesis-stimulating factors (mainly VEGF-A, -B, -C, and -D and platelet-derived growth factors PDGF-A and B) over the anti-angiogenic factors (mainly pigment epithelium-derived factor) causes the expansion of the pathological vessels from the choroid to the area of the BrM [49,50,107,190]. Hypoxia-inducible factor-1 is a key substance in activating the transcription of the pro-angiogenic factors, including VEGF [107,190]. RPE is the main source of pigment epithelium-derived factor, and its decreased expression derives from the degeneration of the RPE cells [190] (Figure 4).

In the degradation of the ECM proteins (as well as in the case of cell growth and survival processes), a crucial role is played by the serine protease HTRA1 (high temperature requirement factor A 1), also called the heat shock protein, which is secreted in stress-related conditions. Expressions of HTRA1 are present in RPE cells, endothelium cells of the choroid, drusen, and subretinal neovascular membranes. HTRA1 is related to early and advanced neovascular AMD and causes an increase in the secretion of metalloproteinases and/or binding the pro-angiogenic factor transforming growth factor-β [191–193] (Figure 5).

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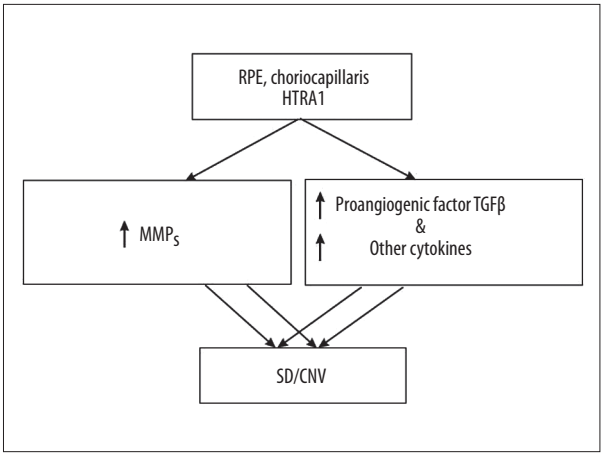

Figure 5. The relation of high-temperature requirement factor A 1 (HTRA 1) to early and advanced age-related macular degeneration. TGFβ – transforming growth factor β.

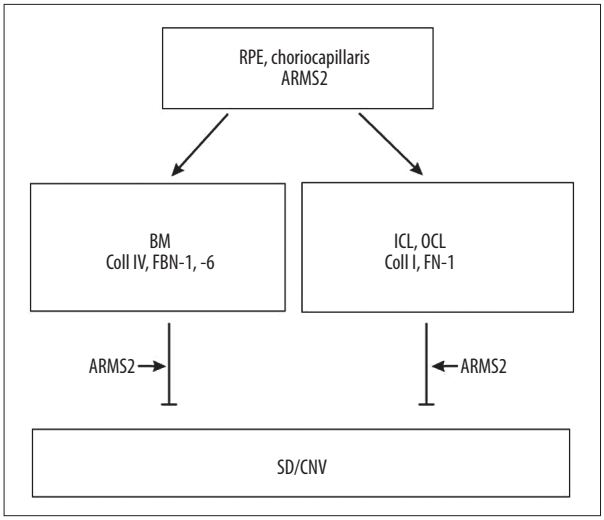

Figure 6. Protective influence of the age-related maculopathy susceptibility 2 protein (ARMS 2) on the structural and functional elements of the extracellular matrix. FBN – fibulins, FN – fibronectin.

Proteins coded by the genes connected with the development of maculopathy (genetically conditioned) include MMP-9 [112]; TIMP-3 [194]; fibulins -3, -5, and -6 [93,95,96,195]; and elastin [17,88], as well as ARMS2 protein [9,196]. The secretory cytosolic (but not the mitochondrial) ARMS2 protein [196] regulates the ECM [9]. It is present in the retina and the RPE; however, it mainly accumulates in the intercapillary spaces of the choroid, where it interacts with elements of the basement membranes, including collagen type IVα2 (COL4A2) and fibulin-1 and -6 (FBLN-1, -6), as well as with ECM proteins, collagen type Iα1 (COL1A1) and fibronectin1 (FN1) [9,90,91]. Homozygous patients, having no ability to synthesize the ARMS2 protein [198], show a higher susceptibility to the development of drusen and AMD [9]. ARMS2 shows functional interaction with the protein network of the ECM; many of these proteins are present in the development of maculopathy [90,91,195,198,199]. The importance of ARMS2 in the pathomechanism of AMD underlines, as pointed out by researchers [9], the direct relationship of ARMS2 to fibulin-6, mutations of which lead to damage in the elastic fibers of the BrM (Figure 6).

The uPAR/uPA system influences the development of advanced neovascular AMD [15]. Both RPE cells and the choriocapillaris epithelium secrete uPAR and inactive uPA [116]. Activated uPA causes the conversion of inactive plasminogen into plasmin (i.e., the protease), which degrades laminin, fibronectin, and other proteins of the ECM [200]. Moreover, uPA also reduces cell adhesion and decreases cellular mobility [98]. uPA, stimulated by, among others, interleukin-1 and other cytokines, synergizes with MMP-9 and elastase in collagen VI and elastin degradation, which in turn enables CNV and the RPE cells to enter the area of the ECM [15]. uPA activity is blocked by 2 endogenous inhibitors (plasminogen activator inhibitors PAI-1 and PAI-2) [200] (Figure 7).

Activation of the pro-renin receptor (PRR), the pivotal element of the renin-angiotensin system, causes an increase in collagen I accumulation, with the level of collagen IV and laminin unchanged, in an animal model [54]. Activation of the PRR receptors does not influence the MMP-2/MMP-14/TIMP-2 complex and therefore does not cause an increase in the levels of collagen IV and laminin, which are the main cause of the development of drusen [54]. As was hypothetically assumed by the authors, activation of PPR may influence the development of early AMD because the increase in collagen I leads to the growth of deposits and to the thickening of the BrM, which together represent early signs of AMD [54]. The increase of PPR expression and collagen I, with unchanged levels of collagen IV and laminin, were also observed in the retinas of patients with hypertension who were untreated during their lifetimes [54]. On the other hand, in the retinas of patients with AMD who were treated for hypertension, an increase in PRR expression and in the amount of collagen I, but a decrease in collagen IV and an unchanged level of laminin, have been demonstrated [54]. Changes in the amounts of collagen I and IV and an unchanged level of laminin are probably induced by drugs that block angiotensin II receptors [54]. In the situation in which AMD occurs simultaneously with hypertension, the crucial pathological regulator of the ECM is angiotensin II. Tests on animals have shown that angiotensin II stimulates the RPE cells to a higher expression of mRNA for the production of the AT1 receptors of angiotensin, the activation of which leads to a greater release of the active form of MMP-2 by the RPE [41]. MMP-2 plays a key role in the early development of AMD as a result of the enhancement of the deposits stored under the RPE layer [41,54]. It has also been shown that in the pathway in which the AT2 receptors

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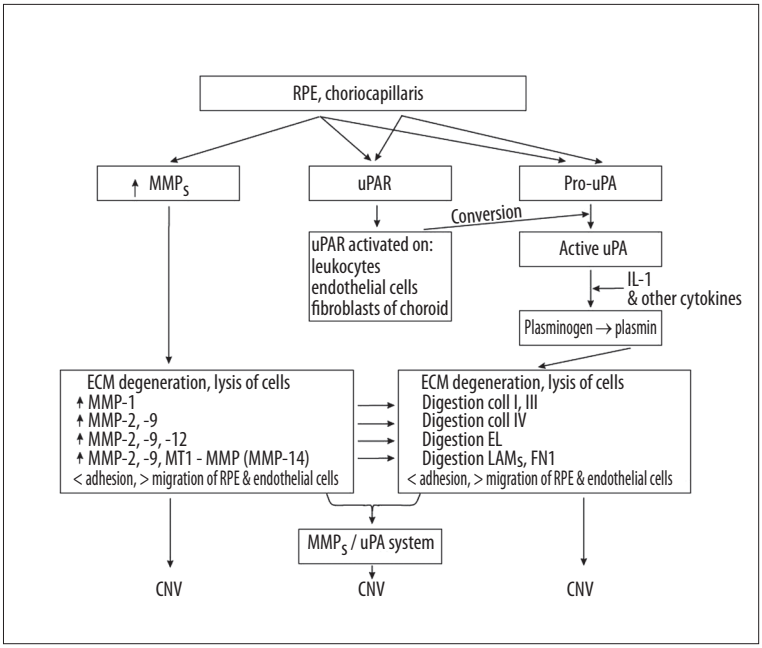

Figure 7. The relationship between the urokinase plasminogen activator receptor/urokinase plasminogen activator system and the development of choroid neovascularization/age-related macular degeneration. IL-1 – interleukin-1, LAMs – laminins, FN1 – fibronectin1.

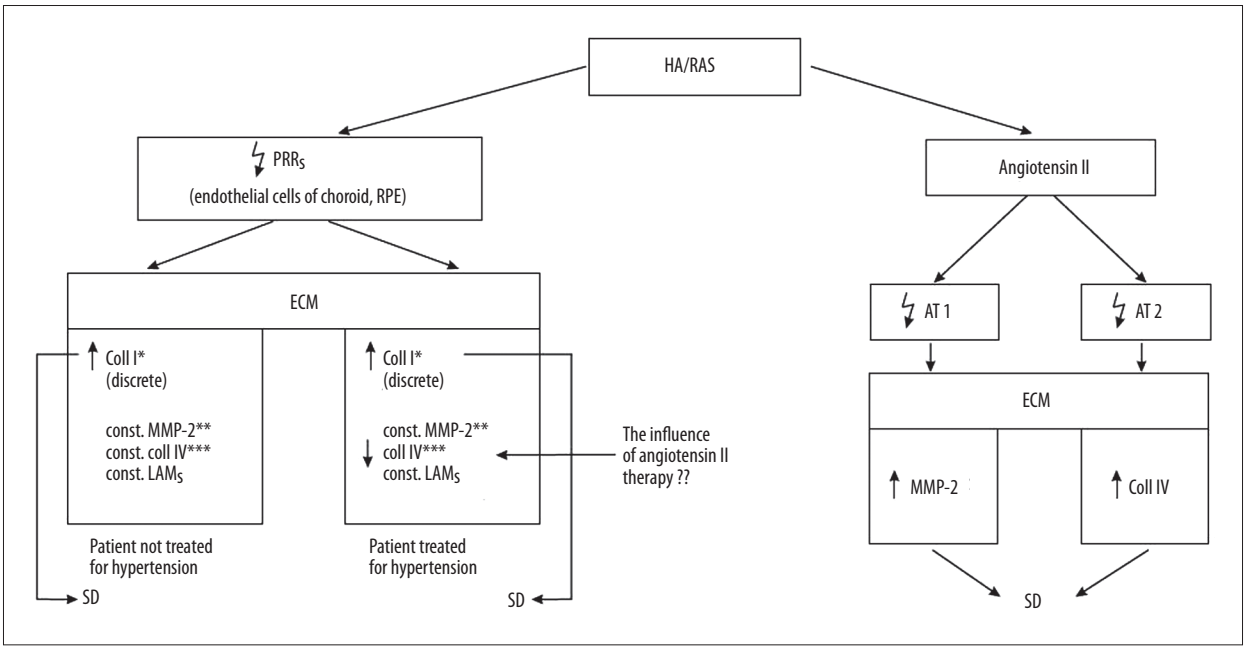

Figure 8. The influence of arterial hypertension (HA) and activated renin-angiotensin system (RAS) on the development of early age-related macular degeneration. PRRs – pro-renin receptors, LAMs – laminins, AT 1,2 – angiotensin receptors 1,2. * Aggravation effect on AMD by favoring accumulation of coll I, but not by stimulating activity of MMP-2; ** when degrading activity of MMP-2 stays unchanged, the synthesis of coll I increases; *** ↑ activation of PRRs do not stimulate the pro-MMP-2/TIMP-2/MMP-14 complex and therefore coll IV and LAMs, the main causes of SD, remain stable.

of angiotensin are activated, angiotensin II stimulates the RPE cells to collect collagen IV [41]. In the case of early AMD occurring together with hypertension, drug-induced blocking of angiotensin II receptors may be of therapeutic importance and at the same time protect against AMD degeneration [41] (Figure 8).

Conclusions

In both early and advanced AMD, the ECM is the area of dynamic changes connected with the activity of its specific regulators – metalloproteinases and their tissue inhibitors. However, it is also under the positive and negative influence of other

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regulatory systems. The importance of the ECM can be seen by the fact that transplants of RPE cells exclusively, without the BrM, do not bring about the required results because, apart from the immunological problems connected with transplant rejection, there also occurs the problem of the ground matrix; the cells are unable to adhere to the age-changed and insufficient BrM and/or are iatrogenically damaged during the surgical removal of the CNV [110]. The ECM has a crucial influence on both the survival and functioning of the transplanted RPE cells [99,110]. We are not able to treat the atrophic form of AMD, and the therapies applied in neovascular AMD (ie, treating neovascularization by means of photodynamic therapy, or blocking its stimulants by drugs injected into the vitreous camera of the eye (pan anti-VEGF Lucentis® or off ophthalmological label pan anti-VEGF Avastin®) may only slow down AMD advancement [201–204]. Better insight into the pathological mechanisms acting in the area of the ECM may lead to the development of new and improved strategies for AMD treatment.

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