Factors determining age-related macular degeneration: a current view

Rasa Liutkevičienė[1], Vaiva Lesauskaitė[2], Virginija Ašmonienė[3], Dalia Žaliūnienė[1], Vytautas Jašinskas[1]

[1]Department of Ophthalmology, Kaunas University of Medicine, [2]Department of Cardiac Pathology, Institute of Cardiology, Kaunas University of Medicine, [3]Laboratory of Neuroscience, Institute for Biomedical Research, Kaunas University of Medicine, Lithuania

Key words: *age-related macular degeneration; risk factors; gene; neovascularization; matrix metalloproteinases.*

Summary. *Age-related macular degeneration affects the macula and is the leading cause of significant and irreversible central visual loss. It is the most common cause of visual loss in people older than 60 years. The pathogenesis of age-related macular degeneration is complex and not completely understood. It is thought that age-related macular degeneration has a multifactorial etiology, the development of which may be caused by interrelation of environmental and genetic factors and body characteristics. In this article, risk factors such as age, gender, cigarette smoking, color of the iris, nutrition, body mass index, oxidative stress, and genetic factors (complement factor H gene, Apo E gene, and others) are reviewed. Here, choroidal neovascularization process, in which hypoxia, inflammatory process, and proteolytic enzymes play a determinant role, is discussed. Considerable attention is paid to genetic polymorphism of matrix metalloproteinases, especially to matrix metalloproteinases 2 and 9, respectively gelatinases A and B, also to matrix metalloproteinase 9.*

Introduction

Age-related macular degeneration (ARMD) affects the macula and is the leading cause of significant and irreversible loss of central visual acuity. Both eyes are always affected, but intensity of damage may be different. ARMD is the most common cause of visual loss in persons aged more than 60 years in the developed countries (1). More than 30% of adults aged 75 years or older have ARMD, and in about 6–8% of the individuals in this age group, the disease progresses and causes the most severe visual loss (2). Epidemiological studies have implicated that in Australia, Europe, North America, the prevalence of ARMD is 0.2% in 55–64-year-old patients and it reaches 13% in 85-year olds (3). Sometimes ARMD can develop in people younger than 40 years.

According to the data of the Blind Register Center, in Great Britain, ARMD as the reason of blindness accounted for approximately 50% of cases (4). According to the data of the Lithuanian Medical Social Expertise Commission, in 2002, 13.8% of people were blind due to ARMD in Lithuania. It took the second place (after glaucoma) in accordance with the data of the Blind Register Center as a primary reason of this disability.

It is estimated that during the period from 1980 to 2020, the projected increase in the elderly population will be 186% in the developed countries and 356% in the developing countries (5). Increasing life expectancy is a natural risk factor for the development of ARMD; accordingly, the aging will determine the increase in the number of the blind. The World Health Organization reports that in 2020, the number of the blind will be around 54 million due to all eye diseases in the elderly over 60 years (5).

Our aim was to review literature, disclose factors determining the development of age-related macular degeneration, and reveal the current view on the pathogenesis of ARMD.

Retinal damage in ARMD

Macular degenerative lesions manifest as drusen formation, changes of the retinal pigment epithelium, lesions of the retinal pigment epithelium and choroidal choriocapillary layer, Bruch's membrane, geographic atrophy of the central fovea, exudative ARMD with choroidal neovascularization, detachment of the retinal pigmentary epithelium, or changes of submacular disciform scarring. Drusen are colloid material (lipids, phospholipids, collagen) excrescences, similar to hyaline, that accumulate in the retina, in Bruch's membrane underlying the retinal pigment epithelium. This process is associated with progressive degeneration of the retinal pigment epithelium and photoreceptors (6). Drusen disturb oxygen metabolism and determine degeneration of photoreceptors, while visual function impairment is as-

Correspondence to R. Liutkevičienė, Department of Ophthalmology, Kaunas University of Medicine, Eivenių 2, 50009 Kaunas, Lithuania. E-mail: rliutkeviciene@gmail.com

Adresas susirašinėti: R. Liutkevičienė, KMU Akių ligų klinika, Eivenių 2, 50009 Kaunas. El. paštas: rliutkeviciene@gmail.com

sociated with the quantity of damaged photoreceptors. In the fovea, where is the largest quantity of photoreceptors, cones dominate, whereas the parafoveal region, where rods dominate, surrounds the fovea. In the early stages, photoreceptors are mostly damaged in the parafovea.

Drusen can be classified as hard and soft. Hard drusen may induce atrophy of the retinal pigment epithelium and choriocapillary layer. Soft drusen may aggregate into clusters and cause exudative macular degeneration and later can induce the detachment of the neuroepithelium. The process progresses, new vessels grow into, leading to exudative hemorrhage. Early ARMD is defined as the presence of drusen and retinal pigmentary abnormalities; late ARMD includes dry ARMD (geographic atrophy of the retinal pigmentary epithelium in the absence of neovascular ARMD) or neovascular ARMD (detachment of the retinal pigment epithelium, hemorrhages, and/or scars).

ARMD is a complex disease involving many factors such as body aging together with the following pathologic changes important in the pathogenesis of this disease: pathogenic oxidative stress, inflammatory processes, changes of the extracellular matrix, changes in biological activity of the retinal pigment epithelium, and genetic factors (7).

Risk factors for age-related macular degeneration

ARMD is a disease of multifactorial etiology, the development of which is determined by environmental risk and genetic factors. The Table presents various factors investigated by different investigators that may have an impact on the development of ARMD. Many investigators have suggested that risk factors cannot be considered as absolutely the only factors inducing development of ARMD.

Epidemiological studies implicate ARMD to be an inherited disease because family members are at increased risk to develop ARMD (8, 9). Twin-based, familial, and other analyses have shown a strong genetic component in the development of ARMD (10). Seddon et al. have shown that prevalence of this disorder among the relatives was significantly higher compared with the prevalence in the control group (11). Similar work done by Klaver et al. has shown that odds ratios for siblings and offspring of ARMD patients were increased compared with siblings of the controls (12). These two large studies indicate that the essential factor determining the development of this disease is inheritance, but unique environmental factors also play an important role.

Genetic factors in the pathogenesis of age-related macular degeneration

Hageman et al. have proposed the hypothesis that inflammation and other factors of the immune response may play an important role in the stimulation of drusen formation and development of ARMD (30). This hypothesis has been confirmed by other researchers (34). Histological examination of the retina of the patients with ARMD has revealed the complement system components in drusen as well as in the choroid (30). Possible pathogenetic links between ARMD and inflammation have also been confirmed by genetic studies. A whole genome study of the patients with ARMD has identified the haplotype of the complement factor H gene, increasing the possibility of developing ARMD (35). The complement factor H is a blood plasma glycoprotein, an important hematologic component controlling the activity of the complement system and protecting the own cells and tissues from damage during the stimulation of the system (36).

It has been revealed by the study performed by Japanese researchers Gatoh et al. in 2006 that the complement factor H gene (1q32) is not the main gene predetermining the development of ARMD in the Japanese population (37).

Gold et al. have studied two independent cohorts consisting of 900 patients with ARMD and 400 control persons, and investigated genetic lesions of two complement system factors, i.e. the variants of the genetic factor B (BF) (6p21.3) and the second complement factor (C2) (6p21.3) (38). The factor B (BF) in one of the more important factors in the alternative stimulation pathway of the complement system. The other factor, C2, is an initial factor in the pathway of the classical stimulation of the complement system. A haplotype analysis has significantly shown one risk (H1) and two protective haplotypes. The variant L9H of the BF gene and the variant E318D of the C2 (H10) as well as C2 variant in the 10 intron and the R32Q variant of the BF(H7) determine lower risk of ARMD (odds ratio is 0.45 and 0.36, respectively) (38). Other researchers have also confirmed a tight link between the genetic injuries of the complement factor B (BF), C2, and C3, and the risk of developing ARMD (39, 40).

The gene of apolipoprotein E (Apo E) is also associated with the development of ARMD. Apo E, which codes the plasma protein participating in the metabolism of cholesterol and other lipids (41), is also found in drusen (42, 43). Its three main isoforms are known differing in one amino acid located at the two primary protein sites and in their function. They are Apo E2 (Cys 112, Cys 158), Apo E3 (Cys 112, Arg 158), and Apo E4 (Arg 112, Arg 158), coded, respectively, by three alleles: epsilon 2, epsilon 3, and epsilon 4 (19 chromosome) (41). Most studies confirm the ApoE ε4 allele to be a protective variant of gene diminishing the risk to develop ARMD (43, 44) and its late form (44), and also reducing the risk of developing the disorder in individuals with a family history of ARMD

Table. The investigated factors that might influence the development of age-related macular degeneration

Factor	Impact	Reference
Age	The strongest known risk factor. The older is the individual, the higher ARMD risk is: 10% of patients aged 66 to 74 years and 30% of patients aged 75 to 85 are diagnosed with ARMD	13
Gender	Women are at higher ARMD risk than men	14
Family predisposition	The more relatives developed ARMD in the family, the higher risk for other family members existed	8, 9
Color of the iris	The brighter the iris, the higher ARMD risk	15
Ethnicity	Caucasians are more often diagnosed with ARMD than black people. Microscopic studies show topographic distribution of lipofuscin and its increased accumulation in the posterior pole of the eye and the macula, and reverse link between the concentrations of lipofuscin and melanin in the retinal pigment epithelium. This inverse relationship is stronger in eyes of Caucasian than in eyes of black population and supports the data of the studies showing that ARMD begins earlier and occurs more frequently in less pigmented eyes	15, 16
Sunlight	There are controversial data: one study suggested that sunlight had no influence on ARMD; however, high-energy visible light influenced its development as it has been found in another research	17, 18
Smoking	Cigarette smoking increases ARMD risk 2 times. A direct relationship has been found between the likelihood of developing the disease and both the smoking duration and number of cigarettes smoked. Smoking is thought to decrease antioxidant levels in the serum, compromise choroidal circulation, and increase oxidative injury to the macula, thus increasing the risk of ARMD	19
Hypertension	High arterial blood pressure increased the risk of developing exudative ARMD by 1.5 times	20
Body mass index	Obese individuals are found to have ARMD twice as frequent	21
Eating habits	High intake of fats, particularly animal, is related to increased risk of ARMD for both men and women. The intake of the fish products (at least twice a week) or any kind of nuts reduces ARMD risk.	21, 22
Oxidative stress	In ARMD patients, lysosomes of the retinal pigment epithelium are believed to accumulate phototoxic pro-oxidative melanin oligomers of low molecular weight that may be partly responsible for the "digestive" speed reduction in the external photoreceptor layer of the retinal pigment epithelium. Decreased "digestive" speed is associated with the formation of lipofuscin and ARMD	23
Antioxidant levels in blood and diet	Low levels of vitamins C, E, carotenoids, zinc, and other antioxidants in blood and nutrition may influence ARMD	24
Increase innflammatory marker levels in blood	ARMD is associated with elevated levels of white blood cells, fibrinogen, oxidized low-density lipoproteins, cholesterol, and C-reactive protein. The increase in blood levels of C-reactive protein and homocysteine is characteristic of ARMD	25, 26, 27, 28
Inflammation	The complement components and immunoglobulins in drusen protein compounds are associated with the deposition of the immune complex (e.g., C5b-9 complex), the so-called acute- phase inflammatory proteins (e.g., amyloid component P and α1-antitrypsin), the proteins modulating the immune response (e.g., vitronectin, clusterin, Apo E, membrane protein factor, complement receptor 1), the major histocompatibility complex class II antigens, HLA-DR antigens and the antigens of cell differentiation. Multinucleated giant cells and leukocytes found in the choroid demonstrate the link between the advanced ARMD and inflammatory process	7, 29, 30
Cataract	There is a probable relationship between cataract and aging process, manifesting as cataract formation with partial nuclear sclerosis and ARMD. Some researchers did not find any link between the cloudy lens and ARMD, whereas the others have revealed a relationship between the lens nuclear sclerosis and ARMD. Some other authors suggested that nuclear sclerosis of the lens was more often observed than cortical cloudiness in the patients with ARMD	17, 31, 32
Cataract surgery	Progression of ARMD in patients with the operated eye due to cataract was more common than in the patients without the intervention. Moreover, late ARMD developed in the operated eyes during 5-year follow-up	31
ARMD in the contralateral eye	Increases the risk of ARMD development in another eye by 87%; 82% of the lesions in another eye occur during 4-year period	33

(45). Meanwhile ε2 allele, on the contrary, is being linked with the greater risk of developing ARMD (44, 46). Souied et al. have offered two different hypotheses explaining the protective mechanism of Apo E 4 in the development of ARMD. Apo E4, in contrast to Apo E 2 and 3, does not contain disulfide bridges; therefore, being smaller, it may be more effectively transported through Bruch's membrane. The other protective mechanism may be explained as follows: Apo E 4 has a positive charge, which diminishes hydrophobicity of the Bruch's membrane and thus contributes to better clearance of the debris (44). It is should be noted that Apo E 4 allele is associated with hypercholesterolemia and greater risk of ischemic heart disease, whereas Apo E 2 allele is considered a protective factor concerning the development of this disorder (46).

Neovascularization of the choroid

In recent years, the blockage of the neovascularization chain has been considered to inhibit the development of ARMD. The vascular endothelial growth factor (VEGF) and the fibroblast growth factor are believed to promote the angiogenesis (46). Meanwhile, it is inhibited by the pigment epithelial factor, angiostatin, endostatin, and other. Neovascularization is mainly induced by retinal hypoxia. Tissue ischemia leads to increased secretion of the VEGF and higher expression of the VEGF R2. The vascular endothelial growth factor causes vasodilatation, increases vascular permeability and protease activity. Such changes allow for the development and expansion of vascular network in the surrounding tissues and its remodeling (47). The fragmentation of the basilar membrane and intracellular connective tissue are essential for the formation of new capillaries. Activated endothelial cells release matrix metalloproteinase (MMP), which, by degrading the basilar membrane, allows capillaries to grow beneath the retina and between retinal layers. Such capillaries often bleed, more liquids are filtered through the walls, and fibrous tissue grows within. Furthermore, the retina swelling and impaired vision occur. MMPs are a family of proteolytic zinc-containing enzymes, which are responsible for degrading extracellular matrix components and play an important role in the physiological and pathological remodeling of tissues (48). MMPs are capable of degrading most of the components of the extracellular matrix, which may play an important role in the extracellular matrix remodeling during angiogenesis. A particular interest has been focused on MMP-9 due to its ability to degrade components of the basement membrane components such as type IV collagen. There are 24 different genes responsible the expression of proteases of MMP family (49). The pathogenesis of age-related macular degeneration is focused on MMP-2 and MMP-9, also known as gelatinase A and B, respectively, due to their ability to cleave gelatin in vitro (heterogeneous compound of soluble proteins, obtained during partial hydrolysis of collagen). For ARMD patients, elevated plasma MMP-9 levels influence the development of choroidal neovascularization (50). Analysis of surgically removed subfoveal fibrovascular membranes from patients affected by ARMD showed MMP-9 expression at the margins of the membrane and in proximity of a thickened Bruch's membrane layer beneath the retinal pigment epithelial cells (51). Chau et al. found no significant difference in plasma MMP-2 levels among the groups of healthy individuals, ARMD patients, and exudative ARMD patients; however, plasma MMP-9 concentrations differed significantly (265±34 ng/mL, 659±315 ng/mL, and 740±494 ng/mL, respectively; P=0.008) (52).

Thus, the increase in MMP-9 expression is characteristic of ARMD. The number of MMP-9 cytosine-adenine (CA) sequences in the promoter region was found to determine the transcription activity, i.e. the gene expression rate (53). Studies with mesangial cells of mice have shown that 24 repeats of CA sequence in the MMP-9 promoter region resulted in up to 20 times higher MMP-9 expression compared with 20 repeats of CA sequence (54). Therefore, in recent years, studies have increasingly focused on the association between polymorphism of MMP-9 microsatellite CA 13–27 sequences in the promoter region and exudative ARMD. An Italian study carried out in the Clinic of Eye Diseases in Trieste University in 2003 found a relationship between the length of MMP-9 promoter microsatellites and choroidal neovascularization in ARMD patients (55). Alleles with 22 or more repeats are more often found in ARMD patients. It has been determined that carriers of one allele with 22 repeats have more than doubled risk of being an ARMD patient. This polymorphism does not cause the disease but increases the MMP-9 expression leading to increased vascular permeability and choroidal neovascularization (55). No difference between the major ARMD risk factors (gender, age, diabetes mellitus, cigarette smoking, and dyslipidemia) and MMP-9 polymorphism was found. A strong linear correlation between longer microsatellites and increased body mass index was the only one association (55).

ARMD is a disease of multifactorial etiology. Its development is determined not only by genetic but also environmental and risk factors. Overall, the most important pathogenetic mechanisms causing the development of the ARMD are the formation of drusen, local inflammation, and neovascularization. Despite current advanced technologies, the factors influencing the initial and subsequent stages of ARMD are still not entirely clear.

Veiksniai, lemiantys amžinę geltonosios dėmės degeneraciją: dabartinis požiūris

Rasa Liutkevičienė[1], Vaiva Lesauskaitė[2], Virginija Ašmonienė[3], Dalia Žaliūnienė[1], Vytautas Jašinskas[1]

[1]Kauno medicinos universiteto Akių ligų klinika, [2]Kauno medicinos universiteto Kardiologijos instituto Kardialinės patologijos klinika, [3]Kauno medicinos universiteto Biomedicininių tyrimų instituto Neuromokslų laboratorija

Raktažodžiai: amžinė geltonosios dėmės degeneracija, rizikos veiksniai, genas, neovaskulizacija, matrikso metalo proteinazės.

Santrauka. Amžinė geltonosios dėmės degeneracija – tai geltonosios dėmės pažeidimas, sąlygojantis negrįžtamąjį centrinio matymo praradimą. Tai dažniausia vyresnių nei 60 metų žmonių aklumo priežastis. Deja, iki šiol nėra visiškai aiškios ligos etiologija bei patogenezė. Manoma, kad amžinė geltonosios dėmės degeneracija yra daugiaveiksnės etiologijos liga, kurios pasireiškimą lemia tiek aplinkos, tiek žmogaus organizmo ypatybinių bei genetinių veiksnių sąsaja.

Straipsnyje trumpai apžvelgiami rizikos veiksniai bei jų vaidmuo amžinės geltonosios dėmės degeneracijos patogenezėje, tokie kaip paciento amžius, lytis, rūkymas, rainelės spalva, mitybos įpročiai, kūno masės indeksas, oksidacinis stresas, genetiniai veiksniai (komplemento H faktorius, apolipoproteinas E ir kiti). Aptarta gyslainės neovaskulizacijos patogenezė, kurioje lemiamas vaidmuo priskiriamas hipoksijai, uždegiminiam procesui bei proteolizinių fermentų veiklai. Didelis dėmesys skiriamas matrikso metalo proteinazėms, ypač matrikso metalo proteinazėms 2 bei 9, atitinkamai želatinazėms A ir B bei matrikso metalo proteinazės 9 genetiniam polimorfizmui.

References

1. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol 2004; 137:486-95.
2. Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, de Jong PT, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004; 122:564-72.
3. Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, et al. Risk factors for age-related macular degeneration: pooled findings from three continents. Ophthalmology 2001; 108:697-704.
4. Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age-related macular degeneration in the United Kingdom. Br J Ophthalmol 2003; 87:312-7.
5. Foster A. Vision 2020: the cataract challenge. J Comm Eye Health 2000;13(34):17-9.
6. Young RW. Pathophysiology of age-related macular degeneration. Surv Ophthalmol 1987;31:291-306.
7. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004;122(4): 598-614.
8. Smith W, Mitchell P. Family history and age-related maculopathy: the Blue Mountains Eye Study. Aust N Z J Ophthalmol 1998(3);26:203-6.
9. Hyman L, Neborsky R. Risk factors for age-related macular degeneration: an update. Curr Opin Ophthalmol 2002;13(3): 171-5.
10. Meyers SM. A twin study on age-related macular degeneration. Trans Am Ophthalmol Soc 1994;92:775-843.
11. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. Am J Ophthalmol 1997;123(2): 199-206.
12. Klaver CC, Wolfs RC, Assink JJ, van Duijn CM, Hofman A, de Jong PT. Genetic risk of age-related maculopathy. Population-based familial aggregation study. Arch Ophthalmol 1998;116(2):1646-51.
13. Tomany SC, Wang JJ, Van Leeuwen R, Klein R, Mitchell P, Vingerling JR, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 2004;11(7):1280-7.
14. Busch H, Vinding T, la Cour M, Jensen GB, Prause JU, Nielsen NV. Risk factors for age-related maculopathy in 14-year follow-up study: the Copenhagen City Eye Study. Acta Ophthalmol Scand 2005;83(4):409-18.
15. Frank RN, Puklin JE, Stock C, Canter LA. Race, iris color, and age-related macular degeneration. Trans Am Ophthalmol Soc 2000;98:109-17.
16. Weiter JJ, Delori FC, Wing GL, Fith KA. Retinal pigment epithelial lipofuscin and melanin choroidal melanin in human eyes. Invest Ophthalmol Vis Sci 1986;27:145-52.
17. West SK, Rosenthal FS, Bressler NM, Bressler SB, Munoz B, Fine SL. Exposure to sunlight and other risk factors for age-related macular degeneration. Arch Ophthalmology 1989;107(6):875-9.
18. Tomany SC, Cruickshanks KJ, Klein R, Klein BE, Knudtson MD. Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam Eye Study. Arch Ophthalmol 2004;122(5):750-7.
19. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye 2005;19(9):935-44.
20. Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 2003;110(4):636-43.
21. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS): AREDS report No. 19. Ophthalmology 2005;112: 533-9.
22. SanGiovanni JP, Chew EY, Clemons TE, Davis MD, Ferris FL, Gensler GR, et al. Age-Related Eye Disease Study Research Group. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study. Arch

Ophthalmol 2007;125(5):671-9.
23. Sarangarajan R, Apte SP. Melanin aggregation and polymerization: possible implications in age-related macular degeneration. Ophthalmic Res 2005;37(3):136-41.
24. Cho E, Stampfer MJ, Seddon JM, Hung S, Spiegelman D, Rimm EB, et al. Prospective study of zinc intake and the risk of age-related macular degeneration. Ann Epidemiol 2001;11(5):328-36.
25. Shankar A, Wang JJ, Rochtchina E, Yu MC, Kefford R, Mitchell P. Association between circulating white blood cell count and cancer mortality: a population-based cohort study. Arch Intern Med 2006;166(2):188-94.
26. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular factors, and age-related maculopathy: Blue Mountains Eye Study. Arch Ophthalmol 1998; 116(5):583-7.
27. Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. JAMA 2004;291(6):704-10.
28. Wine AK, Stader J, Branham K, Musch DC, Swaroop A. Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration. Ophthalmology 2005;112(12): 2076-80.
29. Johnson L, Ozaki S, Staples M, Erickson P, Anderson D. A potential role for immune complex pathogenesis in drusen formation. Exp Eye Res 2000;70:441-9.
30. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res 2001;20 (6):705-32.
31. Klein BE, Klein R, Lee KE. Incidence of age-related cataract: the Beaver Dam Eye Study. Arch Ophthalmology 1998;116: 219-25.
32. Klein R, Klein BEK, Linton KLP. Prevalence of age-related maculopathy: the Beaver Dam Study Eye Study. Ophthalmology 1992;99:933-43.
33. Gudnadottir GS, Magnusson KP, Stefansson E Jonasson F, Helgadottir G, Sigurdsson H. The time pattern of bilateral exudative age-related macular degeneration. Acta Ophthalmol Scand 2005;83(3):333-6.
34. Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in drusen formation and age-related macular degeneration. Exp Eye Res 2001;73(6):887-96.
35. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308(5720):385-9.
36. De Cordoba SR, de Jorge EG. Translational mini-review series on complement factor H: genetics and disease associations of human complement factor H. Clin Exp Immunol 2008;151(1):1-13.
37. Gatoh N, Yamada R, Hiratani H, Renaault V, Kuroiwa S, Monet M, et al. No association between complement gene polymorphism and exudative age-related macular degeneration in Japanese. Hum Genet 2006;120(1):139-43.
38. Gold B, Meriam JE, Zernant J, Hancox LS, Taiber AJ, Gehrs K, et al. Variation in factor B (BF) and complement 2 (C2) genes is associated with age-related macular degeneration. Nat Genet 2006;38(4):458-62.
39. Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM. Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet 2007;39(10):1200-1.
40. Francis PJ, Zhang H, DeWan A, Hoh J, Klein ML. Joint effects of polymorphisms in the HTRA1, LOC387715/ARMS2, and CFH genes on AMD in a Caucasian population. Mol Vis 2008;14:1395-400.
41. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000;1:507-37.
42. Dithmar S, Curcio CA, Le NA, Brown S, Grossniklaus HE. Ultrastructural changes in Bruch's membrane of apolipoprotein E-deficient mice. Invest Ophthalmol Vis Sci 2000; 41:2035-42.
43. Klaver CC, Klifen M, van Duijn CM, Hofman A, Cruts M, Grobbe DE, et al. Genetic association of apolipoprotein E with age-related macular degeneration. Am J Hum Genet 1998;63(1):200-6.
44. Souied EH, Benlian P, Amouyel P, Feingold J, Lagarde JP, Munnich A, et al. The epsilon 4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 1998;125: 353-9.
45. Davignon J, Cohn JS, Mabile L, Bernier L. Apolipoprotein E and atherosclerosis: insight from animal and human studies. Clin Chim Acta 1999;28(1-2):115-43.
46. Lee SH, Schloss GJ, Swain JL. Maintenance of vascular integrity in the embryo requires signaling through the fibroblast growth factor receptor. J Biol Chem 2006;275(43): 33679-87.
47. Švagždys S, Lesauskaitė V. Matrikso metalo proteinazės: piktybinių navikų augimo ir plitimo mechanizmai. (Matrix metalloproteinases: the mechanisms of invasion and metastatic development of malignant tumours.) Medicinos teorija ir praktika 2007;13(2):132-8.
48. Lesauskaitė V, Šinkūnaitė G, Benetis R, Grabauskas V, Vaškelytė J, et al. Matrix metalloproteinase-3 gene polymorphism and dilatative pathology of ascending thoracic aorta. Medicina (Kaunas) 2008;44(5):386-91.
49. Puente XS, Sanchez LM, Overall CM, Lopez-Otin C. Human and mouse proteases: a comparative genomic approach. Nat Rev Genet 2003;4(7):544-58.
50. Westermarck J, Kahari VM. Regulation of matrix metalloproteinase expression in tumor invasion. Faseb J 1999;13: 781-92.
51. De La Paz MA, Itoh Y, Toth CA, Nagase H. Matrix metalloproteinases and their inhibitors in human vitreous. Invest Ophthalmol Vis Sci 1998;39:1256-60.
52. Chau KY, Sivprasad S, Patel N, Danaldson TA, Luther PJ, Chong NV. Plasma levels of matrix metalloproteinases-2 and -9 in age-related macular degeneration. J Hum Hypertens 2003;17(2):119-24.
53. Ye S. Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. Matrix Biol 2000;19:623-9.
54. Fornoni A, Wang Y, Lenz O, Striker LJ, Striker GE. Association of a decreased number of d(CA) repeats in the matrix metalloproteinase-9 promoter with glomerulosclerosis susceptibility in mice. J Am Soc Nephrol 2002;13:2068-76.
55. Fiotti N, Pedio M, Battaglia Parodi M, Atamura N, Uxa L, et al. MMP-9 microsatellite polymorphism and susceptibility to exudative form of age-related macular degeneration. Genet Med 2007;4:272-7.

Received 1 September 2009, accepted 5 February 2010
Straipsnis gautas 2009 09 01, priimtas 2010 02 05