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An impact of mutation on MMP-2, -3 and -9 activity regulation and influence on age-related macular degeneration development: literature review

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Matrix metalloproteinases (MMPs) belong to a family of proteolytic zinc-containing enzymes. Mechanism of MMPs is precisely regulated under normal physiological conditions, but when dysregulated it becomes a cause of many diseases such as arthritis, nephritis, cancer, encephalomyelitis, chronic ulcers, fibrosis, myocardial infarction, age-related macular degeneration (AMD), etc. 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 – the main pathological process associated with age-related macular degeneration development. Activated endothelial cells release matrix metalloproteinases which degrading the basilar membrane allow 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, retina swelling and impaired vision occur.

The article discusses about an impact of mutation on MMP-2, MMP-3 and MMP-9 activity regulation and influence on AMD development.

Key words: age-related macular degeneration, MMP-2, MMP-3, MMP-9 genes, matrix metalloproteinases, polymorphism, pathogenesis

INTRODUCTION

Age-related macular degeneration (AMD) is a multifactorial disorder determined not only by genetic but also environmental and risk factors. Overall, the most important pathogenetic mechanisms causing the development of the AMD are the formation of drusen, hypoxia, local inflammation, which might cause neovascularization. The blockage of the neovas-

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cularization chain has been considered to inhibit the development of AMD. The neovascularization is mainly induced by retinal hypoxia. Tissue ischemia leads to an increased secretion of the vascular endothelial growth factor (VEGF) and higher expression of the VEGF receptor 2. VEGF causes vasodilatation increasing vascular permeability and protease activity. Such changes allow for the development and expansion of vascular network in the surrounding tissues and its remodeling (Svagzdys et al., 2007; Liutkeviciene et al., 2010). The fragmentation of basilar membrane and intracellular connective tissue is essential for the formation of new capillaries. Activated endothelial cells release various matrix metalloproteinases (MMPs) which degrading the basilar membrane allow capillaries to grow beneath the retina and between retinal layers. MMPs, which are found in all organisms, are endopeptidases that contain an active site Zn^{2+} and are divided into subfamilies or clans based on evolutionary relationships and structure of the catalytic domain. MMPs comprise a family of currently 25 related, yet distinct vertebrate gene products, of which 24 are found in mammals (Vihinen et al., 2005; Visse et al., 2003). MMPs are mainly classified into collagenases (MMP-1, -8, -13), gelatinase (MMP-2, -9), stromelysins (MMP-3, -10), membrane-type MMPs (MMP-14, -15, -16, -17), and others (Liutkeviciene et al., 2010; Visse et al., 2003).

In this article we focus on an impact of mutation on MMP-2, -3 and -9 activity regulation and influence on AMD development.

Structure, activity and mutation impact on activity regulation of matrix metalloproteinases (MMP- 2, MMP-3 and MMP-9)

Structure of all known MMPs is similar (Figure). The main components of MMP molecule are:

– signal sequence, which is important for MMPs release from cell propeptide, due to inactiveness of signal sequence of *MMP*;

– catalytic metalloproteinases domen, which include Zn^{2+} ion essential for enzyme activity;

– axial peptide which connects catalytic domain with hemopexin domain;

– hemopexin domain, which determines MMPs possibility to cleave an appropriate substrate (Nagase et al., 2006; Patterson et al., 2001).

Expression of most MMPs is normally low in tissues and is induced when remodeling of extracellular matrix (ECM) is required. Many factors might induce MMPs production: cytokines, growth factors, physical stress, cell–extracellur matrix and cell-cell inter-action (Westermarck et al., 1999). Westermarck et al. found that MMPs activity may be re-

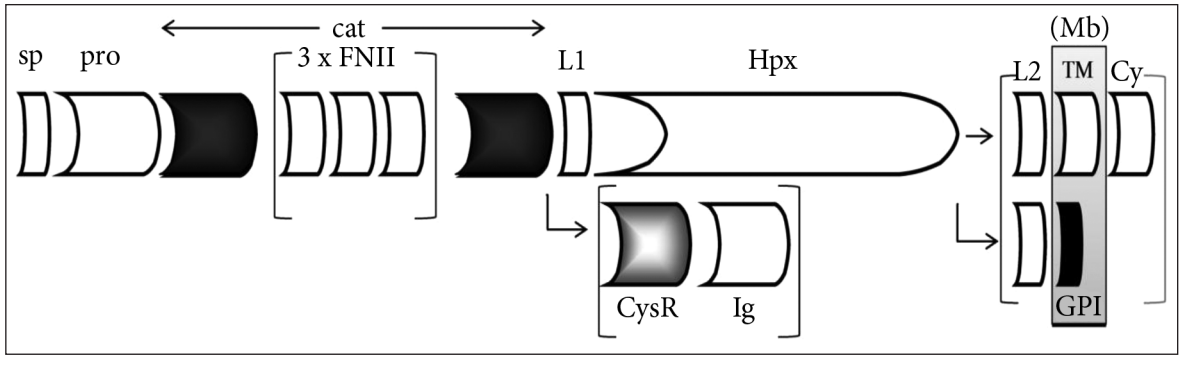

Figure. Matrix metalloproteinases domen structure (Hideaki et al., 2006)

sp – signal sequence; pro – pro-domain; cat – catalytic domain, FNII – fibronectin type II motif; L1 – linker 1; Hpx – hemopexin domain; L2 – linker 2; Mb – plasma membrane; TM – transmembrane domain; Cy – cytoplasmic tail; CysR – cysteine rich; Ig – immunoglobulin domain; GPI – glycosylphosphatidilyinositol anchor7

quired during development and normal physiology in four ways: 1) MMPs may affect cell migration by changing the cells from an adhesive to nonadhesive phenotype and by degrading the ECM; 2) MMPs may alter ECM microenvironment leading to cell proliferation, apoptosis, or morphogenesis; 3) MMPs may modulate the activity of biologically active molecules such as growth factors or growth factor receptors by cleaving them or releasing them from the ECM; 4) MMPs may alter the balance of protease activity by cleaving the enzymes or their inhibitors (Westermarck et al., 1999).

Activation of MMPs expression could be caused by various gene polymorphisms in promoter region, when a binding place of transcriptor factors or other regulating elements is disrupted. *MMP* polymorphisms can be caused by nucleotide changes within promoter region by insertions, substitutions or microsatellite instability (Ye, 2000). In around 90% of cases a single nucleotide polymorphism is determined where one of the basic changes appear in DNA strain (Ra et al., 2007). However, several allele polymorphims can be determined in *MMP* gene promoter regions. Most parts of detected polymorphisms are not biologically active. Only a small part of polymorphisms which changes gene transcription intensity is biologically active, therefore, they may have an impact on genetic predisposition to certain disease (Ye, 2000). A common variant in the promoter region of the human matrix metalloproteinase-3 (*MMP-3*) gene with 1 allele having a run of 5 adenines (5A) and the other having 6 adenines (6A) has an impact on gene expression. *MMP-3* gene is located in chromosome 11 11q22.2-11q22.3 region. Insertion of one adenine (A) in -1171 base-pair position of *MMP-3* promoter causes 6 adenines (6A) formation instead of 5 adenines (5A). It was shown that 6A allele has a higher binding affinity to ZBP-89 transcription factor, which decreases promoter transcription activity and certain gene expression (Ye et al., 1998). *In vitro* methods showed that 5A allele has a higher activity and effect on gene expression compared to 6A allele (Medley et al., 2003). *Ex vivo* method showed that *MMP-3* mRNA and protein activity depends on genotype: 5A/5A shows the highest activity, 5A/6A – the middle activity and the lowest activity shows 6A/6A genotype (Ye et al., 1998; Medley et al., 2003). A mutation (NCBI SNP identification no. rs2285053) which causes an increase in promoter activity was determined in the *MMP-2* (-735) gene promoter transcription region. *MMP-2* gene is located in 16q13-q21 region. The C to T allelic variation located at nucleotide -735 disrupts the Sp1-binding site in promoter region and significantly leads to a low transcriptional activity, therefore T allele has a markedly lower promoter activity than the C allele (Yu et al., 2004). In addition, another C to T allelic variation located in *MMP-2* at nucleotide -1306 (NCBI SNP identification no. rs243865) disrupts the SP1-binding site of transcription factor in promoter region. It is a simmilar effect as it happens for *MMP-2* (-735) gene promoter transcription region mutation (Vasků et al., 2002), where promoter loses 50% activity (Price et al., 2001). A transition of C to T at the 1562 base-pair position upstream of the transcription initiation site (-1562 C/T) of *MMP-9* (NCBI SNP identification No. rs3918242) was shown to have an effect on promoter activity. Transition of C nucleotide to T nucleotide causes more difficulties for nucleic protein complex bind to DNA strain in the presence of T allele. It was determined that once C allele mutates to T allele, a promoter activity increases 1.5 times (Zhang et al., 1999). *MMP-9* gene is located in 20q11.2-q13.1 region. Matrix metalloproteinases are involved in vascular remodeling, and these appear to be active agents degrading extracellular matrix proteins. Their expression on transcription level depends on gene promoter mutations and various transcription factors.

Expression of matrix metalloproteinases in human retina and choroid

Bruch's membrane is a pentalaminated extracellular matrix allowing bidirectional diffusion pathways between the retinal pigment

epithelium and the choroidal blood supply. Aging is associated with progressive thickening due to deposition of matrix components and membranous debris rich in lipids. A consequence of the aging process is an exponential decline in the hydraulic conductivity of Bruch's membrane (Hogan, 1972). Hematoretinal barrier might be disrupted only when a lession in Bruch's membrane or in retinal pigment epithelium occurs. Li et al. found that MMP-3, and MMP-2 and -9 were present in human Bruch's membrane, and that the level of the two inactive gelatinases increased with the age of the donor (Li et al., 1999). Regional differences were apparent in the levels of the two gelatinases. The level of MMP-9 remained invariant, while MMP-2 was lower in the macular region than in the periphery (Li et al., 1999). Given that the thickness of Bruch's membrane increases with age and that of choroid decreases, the observed increase in MMP levels is likely to occur mainly in Bruch's membrane. Cultured retinal pigment epithelium (RPE) cells have been reported to synthesize and secrete MMP-1, -2, -3, and -9 and TIMPs as well. The origin of the various MMPs found in Bruch's membrane and choroid remains unknown. The three potential sources are: 1) RPE cells, 2) choroidal cells, and 3) plasma in the choroidal vessels (Ruiz et al., 1996; Della et al., 1996).

There are two pathways whereby these enzymes may be incorporated into Bruch's membrane. First, the enzymes may be released from plasma, RPE, and / or choroidal cells and then diffuse into Bruch's membrane. This is certainly a possibility for the smaller molecular weight forms such as MMP-1 (52 kDa), MMP-2 (65 kDa), and MMP-3 (57 kDa), because the molecular weight exclusion limit for Bruch's membrane is approximately 65 to 75 kDa. Second, release of MMPs may be coincident with the synthesis of structural components of Bruch's membrane and, therefore may be incorporated passively into the ECM of Bruch's membrane. Such a pathway would allow an incorporation of higher molecular weight enzymes such as MMP-9 (Hussain et al., 1999).

MMP-1, MMP-2, MMP-3, and MMP-9 expression is regulated by various ways such as transcription level, activation of latent MMPs, and inhibition of MMP activity by tissue inhibitors of metalloproteinases (TIMPs) (Chakraborti et al., 2003). TIMPs are known as natural tissue inhibitors, which regulate active and non-active balance of MMP forms. MMPs are initially expressed in an enzymatically inactive state due to the interaction of a cysteine residue of the pro-domain with the zinc ion of the catalytic site. Only after disruption of this interaction by a mechanism called cysteine switch, which is usually mediated by proteolytic removal of the pro-domain or chemical modification of the cysteine residue, the enzyme becomes proteolytically active. Choroidal neovascularization (CNV) is associated with an up-regulation of MMP-9 at the transcriptional level and an activation of pro-MMP-2 by MT1-MMP. This process might be blocked by physiological / natural (TIMP-1 and TIMP-2) and also synthetic inhibitors (Lambert et al., 2003).

MMPs are thought to play a key role during the early phases of choroidal neovascularization. The synthetic inhibitor interacting preferentially with MMP-2, MMP-9, and MT1-MMP (MMP-14) is more efficient comparing to a broad-spectrum synthetic inhibitor in a case of choroidal neovascularisation. MMPs might have contrary functions – induce or block choroidal neovascularisation development (Lambert et al., 2003).

Matrix metalloproteinases (MMP-2, -3 and -9) association with age-related macular degeneration

Studies on the morphogenesis of AMD draw attention to the role of MMPs. These studies have confirmed that ECM dysmetabolism plays an important role in the pathogenesis of AMD (Chong et al., 2005; Spraul et al., 1999) and metabolism of the ECM is closely regulated by MMPs (Lim et al., 2010). The pathogenesis of age-related macular degeneration is mostly focused on MMP-2 and MMP-9, due to their ability to split gelatin *in vitro*.

There are not many studies analyzing MMP-2 influence on AMD development. Some studies analyzed MMP-2 concentration in the blood, some – MP-2 expression, and some analyzed genes' polymorphism in different promoters' regions. To our knowledge, currently there are only two studies analyzing *MMP-2* gene (-1306) C/T polymorphism influence on AMD development (Seitzman et al., 2008; Ortak et al., 2013). The study done by Seitzman et al. analyzed *MMP-2* (-1306) C/T gene polymorphism in females with AMD where association between *MMP-2* and early or late AMD in older women was not found (Seitzman et al., 2008). The second study done by Ortak et al. also analyzed genotype distributions and allelic frequencies of *MMP2* (-1306C>T) (27). No significant differences in either genotype distribution or allelic frequencies of *MMP2* (-1306C>T) were found among the patients with dry AMD, wet AMD and control group (Ortak et al., 2013). An allele of *MMP-2* rs2287074 was less prevalent in subjects with late AMD than in those with early or no AMD ($p = 0.01$) (Seitzman et al., 2008). The third study also proved that analysis of *MMP-2* (-1306 C/T) gene polymorphism has not revealed any differences in the genotype distribution between patients with early AMD and reference group subjects when analyzed in overall group, but *MMP-2* gene C/C genotype was more frequent in AMD patients younger than 65 years comparing to AMD group ≥65 years (67.21% vs. 49.37%, $p = 0.039$), and C/T genotype was more frequent in AMD patients ≥65 years comparing to AMD patients <65 years (26.23% vs. 44.3%, $p = 0.033$) (Liutkeviciene et al., 2013). MMP-2 expression in experimental models (Berglin et al., 2003) and in Bruch's membrane-choroid preparations in human donor eyes with AMD diagnosis were also analyzed (Hussain et al., 2011). Berglin et al. detected low expression of MMP-2 in choroidal neovascularization membrane of mice (Berglin et al., 2003). Accordingly, another group of scientists also found a significant reduction in the development of laser-induced CNV in MMP-2 knockout mice (Plantner et al., 1998). Hussain et al. demonstrated that the total level of active MMP-2 was significantly reduced in Bruch's membrane-choroid preparations of human donor eyes with AMD (Hussain et al., 2011). As positive association between *MMP-2* expression and choroidal neovascularization was observed, on the contrary, a potentially protective role of *MMP-2* in dry AMD was suggested (Cousins et al., 2003). As noted above, estrogen depletion in ovariectomized mice resulted in a loss of *MMP-2* expression and subsequent changes associated with dry AMD, such as sub-RPE deposit formation and Bruch's membrane thickening occurred (Cousins et al., 2003). In other two studies (Chau et al., 2003; Zeng et al., 2013) there were found no differences in MMP-2 concentration between AMD and control group. MMP-2 levels in human plasma among healthy individuals, AMD patients and exudative AMD patients gave a confirmation that the mean concentration of MMP-2 in the early and neovascular AMD was not significantly different from that of the control group (Chau et al., 2003).

MMP-3 is a key member of the MMPs family and plays a central role in the physiological and pathological events associated with connective tissue metabolism and remodeling (Lesauskaitė et al., 2008; Samnegard et al., 2005). Only a few studies have been conducted to clarify if MMP-3 has an influence on retinal vascular remodeling and stiffening, and plays a role in the development of AMD. Literature data concerning MMP-3 effect on AMD are scarce and inconsistent. Some results reveal a possible MMP-3 effect on AMD pathogenesis (Alge-Priglinger et al., 2009), and at the same time are in conflict with controversial data from another study assuming that MMP-3 expression did not play a role on AMD development (Steen et al., 1998). The study analysing MMP-3 gene polymorphism on age-related macular degeneration development in patients with myocardial infarction was carried out as well (Liutkevičienė et al., 2012). The study results revealed that MMP-3 gene polymorphism did not have any predominant effect on the development of AMD in patients with myocardial infarction

(Liutkeviciene et al., 2012). German study showed that MMP-3 expression in the retinal pigment epithelium was induced by oxidative stress (Alge-Priglinger et al., 2009). It is known that oxidative stress is one of the risk factors for the development of AMD, and it is possible that MMP-3 might affect the development of AMD in this way (Liutkeviciene et al., 2012). Swedish researchers conducted a study where the expression of several MMPs, including MMP-3, was analyzed, but no data suggesting MMP-3 involvement in the development of AMD were found (Liutkevičienė et al., 2012).

The studies analyzing an association between MMP-9 and AMD are inconsistent as well. In a few studies, a reduction in MMP-9 was found in choroidal neovascular membranes (Lambert et al., 2002) and in serum (Zeng et al., 2012), while other studies showed an increase in MMP-9 in the aqueous humor (Jonas et al., 2012), plasma (Chau et al., 2007), and choroidal neovascular membranes (Zeng et al., 2004). To our knowledge, only one study done by Fiotti et al. revealed the influence of the MMP-9 genotype, which causes greater gene expression on AMD (Zeng et al., 2004). This study found a relationship between the length of *MMP-9* gene promoter microsatellites and choroidal neovascularization in AMD patients (Fiotti et al., 2007). It has been determined that carriers of one allele with 22 repeats have more than double the risk of AMD. This polymorphism does not cause the disease but increases the MMP-9 expression leading to increased vascular permeability and choroidal neovascularization (Fiotti et al., 2007). No difference between the major AMD risk factors (gender, age, diabetes mellitus, cigarette smoking, and dyslipidemia) and *MMP-9* polymorphism was found. The logistic regression analysis showed that the status of carrier of a microsatellite 22 repeats was the only variable entering into the equation (P = 0.011). The single association was high body mass index value which is linked to a higher risk of developing AMD (Fiotti et al., 2007). The number of cytosine-adenine (CA) sequences in the *MMP-9* gene promoter region was found to determine the transcription activity (Ye, 2000). Studies with mice mesangial cells have shown that 24 repeats of CA sequences in the *MMP-9* gene promoter region result in up to 20 times higher MMP-9 expression compared with 20 repeats of CA sequence (Fornoni et al., 2002). Furthermore, the results of the study by Steen et al. revealed an importance of MMP-9 together with MMP-2 expression at the areas of new vessel formation and at the enveloping of the Bruch-like membrane, suggesting that MMP-9 and MMP-2 may be cooperatively involved in the progressive growth of choroidal neovascular membranes in AMD (Steen et al., 1998). Lambert et al. demonstrated a significant reduction in the development of laser-induced choroidal neovascularization in MMP-9 knockout mice suggesting that MMP-9 may be important in the pathogenesis of AMD (Lambert et al., 2002), and in Bruch's membrane-choroid preparations from donor eyes, the total level of active MMP-9 was significantly reduced too (Hussain et al., 2011). Interestingly, a recent study reported that MMP-9 was significantly elevated in the aqueous humor of patients with neovascular AMD (Jonas et al., 2012) and in the plasma in AMD and CNV groups (Chau et al., 2003). Zeng et al. showed different results and demonstrated no relationship between the increased levels of circulating MMP-9 and AMD (Zeng et al., 2013). Chau et al. found opposite results and proved that the mean plasma levels of MMP-2 were not significantly different in the three groups but the mean plasma MMP-9 levels were significantly higher in AMD and CNV groups compared to that of the control group (265 ± 134 ng/mL, 659 ± 315 ng/mL, and 740 ± 494 ng/mL (p = 0.008)) (Chau et al., 2007). To our knowledge, there is only one study analyzing the impact of *MMP-2, MMP-3*, and *MMP-9* genes polymorphism on the development of early AMD. This study proved that the frequency of the *MMP-2* (-735) C/T and *MMP-3* (-1171) 5A/6A genotypes did not differ significantly between the patients with early AMD and the control group, while the *MMP-9* (-1562) C/C genotype was more frequently detected in patients with AMD than

the control group (73.7% vs. 64.6%, $P = 0.048$) (Liutkeviciene et al., 2013). The logistic regression analysis showed that the *MMP-9* (-1562) C/C genotype increased the likelihood to develop early AMD (OR = 1.51, 95% CI: 1.01–2.21; $P = 0.046$). After the subdivision into the groups by age, a significant difference only in the frequency of the *MMP-9* (-1562) C/C genotype was found comparing the AMD patients and the control group younger than 65 years (79.7% vs. 66.4%, $P = 0.039$) (Liutkeviciene et al., 2013).

CONCLUSIONS

Age-related macular degeneration is a multifactorial disorder. Alteration of matrix metalloproteinases plays a very important role in AMD pathogenesis, especially in the early phases of choroidal neovascularization. During pathological process MMP-2, MMP-3 and MMP-9 present in human Bruch's membrane and RPE at different level and position are involved in inflammatory process. MMP-2, MMP-3, and MMP-9 expression are regulated by various ways: as a transcription, activation of latent MMPs, and inhibition of MMP activity by tissue inhibitors of metalloproteinases. However, MMP-2, MMP-3 and MMP-9 action facts in AMD pathogenesis are still controversial therefore further research is necessary.

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MUTACIJŲ POVEIKIS MMP-2, MMP-3 IR MMP-9 GENŲ AKTYVUMO REGULIAVIMUI IR AMŽINĖS GELTONOSIOS DĖMĖS DEGENERACIJOS PASIREIŠKIMUI: LITERATŪROS APŽVALGA

Santrauka

Matrikso metaloproteinazės (MMP) priklauso proteolizinių fermentų šeimai, kurios sudėtyje yra cinko. MMP tikslūs reguliavimo mechanizmai vyksta normaliomis fiziologinėmis sąlygomis, tačiau joms sutrikus gali pasireikšti daugelis ligų, tokių kaip artritas, nefritas, vėžys, encefalomielitas, lėtinės opos, fibrozė, miokardo infarktas, amžinė geltonosios dėmės degeneracija (AGDD) bei kitos. MMP skaido ir modifikuoja beveik visus užląstelinio matrikso komponentus ir yra svarbios matrikso

remodeliacijoje užląstelinės angiogenezės metu, o tai – pagrindinis patologinis procesas, susijęs su amžinės geltonosios dėmės degeneracijos reiškiniais. Aktyvuotos endotelio ląstelės atpalaiduoja matrikso metalo proteinazes, kurios, ardydamos bazinę ląstelės membraną, sudaro sąlygas kapiliarams įaugti po tinklaine ir tarp tinklainės sluoksnių. Iš tokių kraujagyslių dažnai kraujuoja, jų sienelės praleidžia skysčius, auga fibrozinis audinys, tinklainė paburksta, blogėja regėjimas.

Šiame straipsnyje aptariame mutacijų poveikį MMP-2, MMP-3 ir MMP-9 genų aktyvumo reguliacijai ir poveikį AGDD reiškiniams.

Raktažodžiai: amžinė geltonosios dėmės degeneracija, MMP-2, MMP-3, MMP-9 genai, matrikso metaloproteinazės, polimorfizmas, patogenezė