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Review article

MMP targeting in the battle for vision: Recent developments and future prospects in the treatment of diabetic retinopathy

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ABSTRACT

Matrix metalloproteinases (MMPs) are enzymes capable of degrading nearly all types of extracellular matrix. They perform a wide range of roles in physiological processes, which is the reason for their strict regulation by numerous mechanisms including natural tissue inhibitors of metalloproteinases (TIMP). Research only started to shed light on more troublesome aspects of MMPs function, like cancer progression, Alzheimer's disease, atherosclerosis, ageing. Moreover, their profound role in diabetes is being carefully investigated including one of its most debilitating complications - diabetic retinopathy (DR), the leading cause of acquired blindness worldwide. Traditional treatment of this condition seems to be only mildly satisfactory, which elicited substantial interest in the field of new therapeutic methods including MMP targeting. So far, significant roles of MMP-2 and MMP-9 in the development of retinopathy have been established, with special attention given to the process of blood-retinal barrier impairment. Further exploration revealed MMP-10 and MMP-14 involvement as well as changes in MMP/TIMP ratio.

In this review, we provide insight into MMPs role in diabetic retinopathy with a clarification of various mechanisms regulating MMP activity in the light of the recent studies. We conclude with an overview of novel DR therapies targeting MMPs and point to the need of further examination of their usefulness in clinical setting, with an eye towards future research.

1. Introduction

1.1. Diabetes as a worldwide threat

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders in the world. Undoubtedly, it is becoming a major threat to global health with an estimated 592 million people living with this disease by 2035 [1]. Although diabetes mellitus is a much more heterogeneous disease, it can be subdivided into type 1 and definitely more common type 2. Type 1 diabetes (T1D) occurs as a consequence of autoimmune destruction of insulin-secreting β cells in the islets of Langerhans within the pancreas. Whereas, type 2 diabetes (T2D) is associated with increased insulin resistance and features of metabolic syndrome – i.e. obesity, dyslipidemia and hypertension [2,3].

Although diabetes might be a cause of acute disorders, physicians worldwide encounter most often chronic complications of this disease, out of which the most diversified are vascular ones. They can be generally divided into micro- (retinopathy, neuropathy and nephropathy) and macroangiopathies (ischemic heart disease, peripheral vascular disease and cerebrovascular disease) [4].

1.2. Diabetic retinopathy: the breakdown of the blood-retinal barrier

Retinopathy remains one of the most debilitating microvascular complications of diabetes and the leading cause of acquired blindness affecting approximately 4.2 million people worldwide, with projections of up to 191 million people affected by 2030, globally [5,6]. Almost all individuals with type 1 diabetes, and more than two-thirds with type 2 diabetes, suffer from some form of retinopathy within 20 years of diabetes [7].

Our knowledge has been greatly enriched by extensive research in the field of the pathogenesis of diabetic retinopathy. Oxidative stress, genetic factors, inflammation, increased formation of advanced glycation end products, activation of polyol pathway and protein kinase C have all emerged as possible mechanisms in the development of diabetic retinopathy. Unfortunately, the exact underlying mechanism still

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remains elusive [8,9].

The above-mentioned processes lead to increased vascular permeability, a hallmark of diabetic retinopathy that occurs during the early stages. Furthermore, retinal blood vessels begin to weaken due to the loss of pericytes. It all results in the breakdown of the blood-retinal barrier (BRB) and leakage of plasma from bloodstream into the retina causing swelling that leads to hypoxia [6,10–12]. Hypoxia leads to the secretion of a various angiogenic factors, out of which the most important is vascular endothelial growth factor (VEGF) [13,14].

Thus, non-proliferative diabetic retinopathy, which is also characterized by microaneurysms and hemorrhages progresses slowly to proliferative stage where the new blood vessels begin to develop on the retina, optic nerve and iris. The fragility of these vessels makes the patient vulnerable to retinal hemorrhages. Moreover, the accumulation of fluid in subretinal space due to leakage may result in macular oedema and, subsequently, retinal detachment. This complication might occur in every stage of diabetic retinopathy and is a major cause of acute vision loss in diabetic patients. If not treated, changes in microcirculation result in chronic condition, known as ischemic diabetic maculopathy. It stays, however, unclear, how and whether the intensity of neovascularization is connected with chronic vision loss in the course of diabetes [6,10–12]. The presence of retinopathy reflects the disease duration and the degree of glycemic control. That is why the importance of „tight" blood glucose control should be emphasized as it reduces the incidence and progression of retinopathy [6,7,15].

All the morphological changes we mentioned are presented in Fig. 1.

2. Matrix metalloproteinases: main enzymes implicated in ECM degradation

Matrix metalloproteinases (MMPs), also called matrixines, are zinc-dependent endopeptidases, which perform enzymatic activity in extracellular matter [16–18]. All types of ECM, with the exception of polyglycan, can be degraded by them [19]. As a class of enzymes, MMPs possess similar structure, which comprises of 3 domains: pro-peptide, proteolytic and hemopexine-like one [20,21]. The secretion of most MMPs as inactive pro-enzymes, is then followed by the cleavage by plasmin to active forms [22].

Fig. 2 provides MMPs' structures with detailed description.

Vertebrates have genes for 28 matrixines, out of which at least 23 MMPs are produced in human [23]. Regarding their chemical substrates or function, some of them are grouped under trivial names: collagenases, gelatinases, stromelysines or membrane

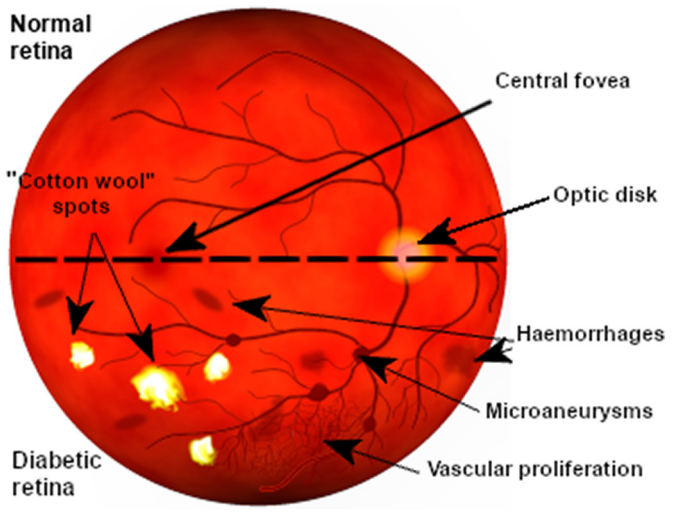

Fig. 1. Schematic representation of normal retina and morphological changes visible during fundoscopy in the course of PDR.

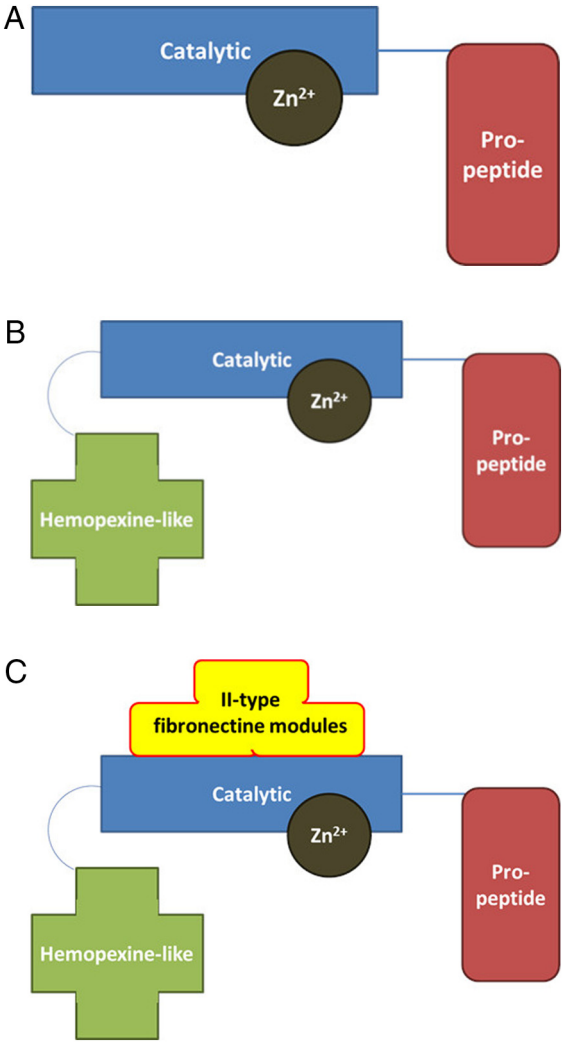

Fig. 2. Structure of matrix metalloproteinases. (A) Minimal domain MMP: MMP-7 (B) single hemopexin –domain MMP: MMP-1,3,8,10,12,13 (C) gelatinases: MMP-2,9.

metalloproteinases [12]. Biological effects and substrate specificity for particular MMPs are presented in Table 1.

Although their proteolytic activity in ECM was being examined as early as in 1960s [24], recent years have seen growing attention to MMPs from many medical researchers worldwide. As their main tasks in living organisms involve proper wound healing and ECM turnover, such functions were the first to be discovered and are currently relatively well-researched [25,26].

Despite that, there is still much inconsistency in less known functions of MMP, which include activation or deactivation of various cellular receptors. Indeed, apart from simple removal of various extracellular proteins, MMPs are able to activate or deactivate cellular machinery from outside and lead to intracellular changes. Surprisingly, some of them take part in activation and deactivation of various hormones and signal molecules. As they work out biological activity not only extra- but also intracellularly, they may connect such different processes as embryogenesis or immunoregulation [20,21,27].

Nonetheless, the role of MMPs is not always glorious – they are proved to be involved in progression of cancer, atherosclerosis, inflammatory bowel disease, Alzheimer's disease, ageing processes and, last but not least – diabetes mellitus [27–30]. Such a striking ambiguity of MMPs deserves further attention and therefore will be studied thoroughly in this paper.

Table 1
Biological effects and substrate specifity of metalloproteinases.

Group	Name	Other names	Production	Substrates	Main functions	References
Collagenases	MMP-1	Interstitial/fibroblast collagenase	Fibroblasts, Endothelial cells, monocytes	Collagen (I,II,III,V,X), gelatin MMP-2, 9	Tissue remodelling, metastases	[24,25,33]
	MMP-8	Neutrophil collagenase	Neutrophils, macrophages	Collagen (I,II,III,V,X) proteoglycans, gelatin	Wound healing, leukocyte migration	[24,25,33]
	MMP-13	Interstitial collagenase	Fibroblasts	Collagen (I,II,III, X), laminin, proteoglycans	Bone remodelling	[24,25]
Stromelysines	MMP-3	Stromelysin-1	Fibroblasts, epithelial cells	Collagen (III,IV,IX), proteoglycans, fibronectin, elastin	Limiting plaque growth, neoplasm initiation	[22,24,25,33]
	MMP-10	Stromelysin-2	Epithelial cells, fibroblasts	Collagen (III, V,X), laminin, casein, fibronectin	Atherosclerotic vascular remodelling, inflammatory bowel disease	[22,25,29]
Metalloelastases	MMP-12		Macrophages, osteoclasts	Collagen IV, elastin, fibronectin, proteoglycans, plasminogen	Macrophage migration, emphysema	[22,24,25]
Transmembrane	MMP-14	MT1-MMP	Many cell types	Collagen I,II,III, fibronectin, laminin, vitronectin	Angiogenesis, malignant transformation, cell migration	[19,24,26,33]
Gelatinases	MMP-2	Gelatinase A	Fibroblasts myocytes endothelium	Collagen I,II,III,IV,V,X elastin, fibronectin, gelatin	Cell migration, vascularization, cancer invasion and metastasizing, bone development	[20,24,26]
	MMP-9	Gelatinase B	Monocytes, neutrophils	Collagen (IV,V,X), elastin, gelatin, IL-8, fibronectin, IL-1B, plasminogen	Angiogenesis, cell migration, bone development, pro-inflammatory	[20,24–26,30]
Minimal domain	MMP-7	Matrilysin 1	Glandular epithelial cells in skin, endometrium, mammary gland, prostate	Collagen I, IV, plasminogen, β-chain of insulin	Vasoconstriction and cell growth endometrium involution, innate immunity, wound healing, tumor growth and invasiveness	[24,25,33]

3. How to maintain the golden mean in MMP activity: Tissue inhibitors of metalloproteinases

The activity of MMPs, if unlimited, would be potentially devastating for the organism. On that account, the processes of synthesis, activation and degradation of matrixins are performed in a precisely organised way. Apart from many intracellular modulators of MMP expression (such as H-Ras, etc.) there are also extracellular inhibitors of proteolysis [31,32].

Tissue inhibitors of metalloproteinases (TIMPs) play an important role as endogenous inhibitors that are capable of binding MMPs in a specific manner and impeding their activation. So far, four types of TIMPs: TIMP-1, TIMP-2, TIMP-3, and TIMP-4 have been identified [33]. All of the TIMPs perform similar functions, although there are some differences concerning their specificity. For instance, TIMP-2 is two to ten times more effective than TIMP-1 in the inhibition of MMP-2. Whereas, TIMP-1, unlike TIMP-2 and TIMP-3, cannot effectively degrade membrane-type MMPs (MT-MMPs) [34,35].

Apart from MMP deactivation, TIMPs can be also activating factor in some cases. TIMP-2 forms an activating complex for proMMP-2, while TIMP-1 forms similar complex with proMMP-9 [35].

TIMPs bind to corresponding MMPs with stoichiometric ratio 1:1, thus the balance between MMP and TIMP concentrations is precisely regulated on various levels [33,36]. Given the chronic inflammation, it might be expected that diabetic individuals exhibit higher concentrations of MMPs in plasma and tissue samples. However, data on MMPs and TIMPs concentration are not consistent [37–39]. In most cases MMP/TIMP proportion is elevated [29,40,41]. This phenomenon is often considered to be the cause of various pathological conditions, including chronic diabetic complications [38]. On the other hand, some diabetic complications involve lowering of MMP activity. This applies to diabetic nephropathy, probably due to increased glycation-related activity of TIMP-2, the main inhibitor of MMP-2 [42,43].

Currently, the most extensive research concerns TIMP-1. Probably, TIMP-1 might prevent the occurrence of diabetes mellitus type 1, which was stated in in vivo study. It was observed that overexpression of TNF-related Apoptosis-Inducing Ligand (TRAIL) elevates the TIMP-1 production. Inhibition of MMP activity, caused by TIMP-1, leads to the decrease in the migration of cytotoxic T cells into the pancreatic islets and prevents cytokine-induced apoptosis, which might constitute an attractive therapeutic approach in the future [44,45].

Peeters et al. suggest in their study that TIMP-1 may be characteristic of abnormal regulation of matrix remodelling after cardiovascular events [37]. Such a conclusion is supported by studies in animal models that show the association between the elevation of plasma TIMP-1 and increased cardiac fibrosis, left ventricular hypertrophy, and cardiac dysfunction in type 1 diabetic minipigs [46].

Nevertheless, a thorough analysis of current advances in the field of medical applications of TIMP greatly exceeds the scope of this review.

4. MMP roles in angiopathies – a brief overview

Although each of macro- and microangiopathies involve changes in MMP concentration, their exact role in these processes seems to be ambiguous. This section summarises recent reports on MMP function in terms of vascular complications other than diabetic retinopathy.

Of particular value is the fact that increased renal expression of MMP-2 was observed in the early phase of diabetic nephropathy [37,47]. It might be explained by the fact that MMP-2 could be protective against albuminuria by inhibiting ECM accumulation [47]. In addition, the expression of MMP-5, which converts pro-MMP-2 to its active form, was upregulated in diabetic kidney tissue samples of patients [48]. Besides, in the view of the latest studies MMP-7 might serve as a biomarker for renal fibrosis [49,50].

Simultaneously decreased level of MMP-2 activity/expression in diabetes is significantly associated with cardiac fibrosis, which leads to

the diastolic dysfunction, and later the systolic dysfunction [51,52]. McKittrick et al. suggest in their study that urinary activity of MMP-2 as well as MMP-9 and its complex with neutrophil gelatinase-associated lipocalin (NGAL/MMP-9) may serve as useful biomarkers for predicting vascular remodelling in diabetic renal and vascular complications [53].

Furthermore, MMP-2 plays also a crucial role in diabetic neuropathy. Although, increased expression of MMPs is related to neuropathic pain [18], MMPs play vital roles in Wallerian degeneration and nerve regeneration [54]. Ali et al. showed that the level of MMP-2 is reduced in the peripheral nerves in diabetic rats, which might contribute to the regenerative deficits in this metabolic disease. Moreover, it appears to be an important pathogenic mediator in this pathological process [49,50]. Therefore, enhancement of MMP-2 expression/activity may be a therapeutic target for the treatment of early diabetic nephropathy, as well as neuropathy [47,54].

On the other hand, MMPs are responsible for the increased matrix degradation within the atherosclerotic plaque leading to the formation of unstable plaque, and, as a consequence, cardiovascular events, especially when an imbalance between MMPs and TIMPs exists [55–58]. Goncalves et al. revealed that MMP-12 levels are particularly associated with atherosclerotic burden [59]. In the same time, Martinez-Aguilar et al. indicated that MMP-10 activity also contributes to cardiovascular complications of diabetes due to high expression within atherosclerotic plaques [60]. In addition, Montero et al. reported the link between elevated CRP levels and atherosclerotic plaque destabilization caused by the MMP-1 and MMP-10 activities [61].

Notwithstanding the role of MMP-10 and MMP-12, they are not the only ones implicated in cardiovascular events. The levels of MMP-9 appear to be significantly increased during acute coronary syndromes in diabetic patients when compared to nondiabetic patients [17,55,62]. Serum level of MMP-9 has been suggested as biomarker in differentiation of patients with unstable angina with plaques from those with unstable angina but without plaques [63]. Similar study in the search for a novel biomarker was conducted by Leeuw et al. According to them, MMP-3 is one of the most accurate factor in predicting cardiovascular events [64].

Furthermore, the increased activity of MMPs in diabetes causes degeneration of elastic fibers in vessels. The degraded elastic fibers tend to induce calcium deposition, which in turn leads to arterial stiffening and the progression of coronary artery disease [65]. The strongest association concerns MMP-2. It is explained by the ability of MMP-2 to release transforming growth factor β (TGF-β) from the ECM, thus leading to the increase in fibroblast-mediated ECM production [66]. Another factor that contributes to the increased incidence of coronary disease in diabetic patients is the reduced blood vessel formation. The impairment of angiogenesis results from its suppression by angiostatin, generated by MMP-2 and -9 via proteolytic cleavage of plasminogen [67].

5. MMP roles in diabetic retinopathy - current state of the field

In diabetic retinopathy, the balance of MMPs becomes disrupted [68,69]. Since MMPs are leading determinants of extracellular matrix degradation, their role in retinopathy is significant. They attribute to increased vascular permeability by degrading the junction proteins, occludin and cadherin that are important to maintain the BRB junction complex [7,12,36,70].

Particular attention has ever been paid to the role of MMP-2 and MMP-9 as they belong to the group of collagenases, enzymes that are capable of degrading basement membranes. Furthermore, they play an important role in neovascularization [7,16,68,71]. Giebel et al. reported that retinas of rats with 12 weeks of diabetes demonstrated elevated mRNA levels of three MMP members, MMP-2, MMP-9 and MMP-14. They also stated the increased production of MMP-9 when retinal endothelial and pigment epithelial cells were exposed to high glucose conditions [72]. Further research was conducted by Navaratna et al. who observed the increased levels of MMP-2 and MMP-9 in isolated retinal vessels of animals with only 2 weeks of diabetes. What is more, they corroborated a crucial role of MMPs in the disruption of blood-retinal barrier with the use of BB-94, MMP inhibitor that effectively suppressed retinal vascular permeability [70]. Descamps et al. discovered that active MMP-9, found in the vitreous humour of patients with proliferative diabetic retinopathy, was associated with vitreous haemorrhage [73]. The research conducted on the small group of patients cast doubt on the importance of MMP-9 in diabetic retinopathy [68]. However, the direct role of MMP-9 in the development of diabetic retinopathy has been confirmed since Kowluru et al. discovered that the abrogation of MMP-9 gene protected against the development of this complication in diabetic mice [74]. Then, Ishizaki et al. reported that the regulation of MMP-9 is dependent on angiotensin II, as well as VEGF. As a result, ACE-dependent angiotensin II formation and VEGF might take part in the increase of MMP-9 concentrations in the vitreous of eyes with PDR [75]. Further research conducted by Abu El-Asrar et al. revealed that MMP-9 is not only dependent but it might play an essential role in neovascularisation as it stimulates the production of VEGF, as well as the proteolytic release of VEGF from ECM-associated reservoirs [14]. Furthermore, it was suggested that the increased expression of MMP-9 in PDR might cause the reduction of the tissue factor pathway inhibitor (TFPI) expression. TFPI might be capable of inhibiting angiogenesis according to the data from animal studies [14]. In 2018 Abu El- Asrar et al. demonstrated one more time a positive correlation between the vitreous levels of MMP-9 and VEGF in patients with PDR, but also investigated the expression of all four TIMPs. They detected the increase of TIMP-1 and TIMP-4 levels in the vitreous fluid from patients with PDR, as well as their significant positive correlation with the levels of MMP-9 and VEGF [76].

Their results remain in accordance with the previous reports that also detected increased levels of TIMP-1 in the vitreous of patients with PDR [71,73]. Thus, the insight into the role of TIMPs might be indispensable in identifying new medications targeted to the modulation of MMPs and TIMPs. These all associations are summarised in Fig. 3.

Another MMP that deserves to be mentioned is MMP-1 as Abu El-Asrar et al. found MMP-1 in 40% of vitreous samples from patients with PDR; in contrast, no samples from nondiabetic patients contained it. What is more, a significant positive correlation between vitreous fluid level of MMP-1 and VEGF was detected as well. It suggests that thrombin/MMP-1/protease-activated-receptor-1 pathway is probably involved in ischemia-induced angiogenesis in PDR [77].

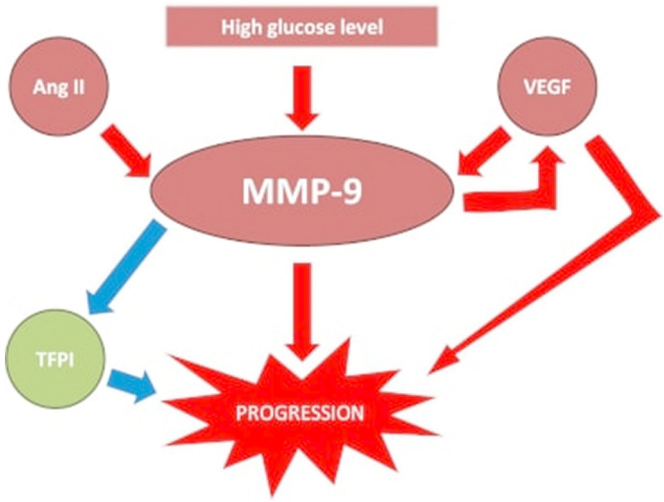

Fig. 3. Relation of MMP-9 and other mediators and their impact on DR progression; red arrows – stimulation, blue arrows – inhibition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

During their search for other MMPs that might constitute targets for treatment, Toni et al. investigated the role of MMP-10 in diabetic retinopathy and nephropathy. They proved that matrix metalloproteinase-10, which was best known for enhancing tissue plasminogen activator fibrinolytic activity, was also strongly and positively associated with PDR and diabetic nephropathy. Of particular value is the fact that they also demonstrated that the absence of MMP-10 ceased the development of these complications in STZ-induced murine diabetes model [69]. Moreover, Matsumura et al. stated that vitrectomy could cause abnormally higher concentrations of MMP-10 in the tears of diabetic patients [78].

Although MMP-14 was reported to be a regulatory factor in angiogenesis years ago [79], it was 2018 when Abu El-Asrar et al. showed for the first time that this transmembrane collagenase was significantly increased in the vitreous fluid from patients with PDR, as well as in the retinas of diabetic rats. Moreover, they observed positive correlations between the levels of MMP-14 and the levels of MMP-9 and VEGF, a key factor in angiogenesis [80].

In comparison with the above-mentioned MMPs, the role of MMP-2 has remained controversial. In some studies researchers elucidated the plausible mechanism by which MMP-2 resulted in the apoptosis [81]. Mohammad et al. have shown that incubation of retinal cells in high glucose makes them upregulate the MMP-2 and MMP-9 expression. Therefore, inhibition of MMP-2 and MMP-9 enables to prevent retinal capillary cell apoptosis [12]. What is more, Peeters et al. discovered a significant positive correlation between high levels of MMP-2 and the severity of retinopathy [37]. Whereas, other studies did not report any differences in levels of MMP- 2 between nondiabetic control patients and PDR patients [82].

6. Novel therapies targeting MMPs – recent developments and future prospects

6.1. In the search for the most effective methods of treating DR

As diabetic retinopathy is a significant diabetic complication and potentially growing burden on health systems around the world, early diagnosis and therapy seems indispensable to reduce the magnitude of this problem, with a wide range of treatments available.

The extant therapeutic methods used in diabetic retinopathy, like anti-VEGF intravitreal injections, surgery or laser therapy, are quite effective and considered to be the benchmark by which other methods are judged [83]. However, these approaches sometimes fail to prevent vision loss and usually do not improve patients' vision. Therefore complimentary or alternative treatment options are being studied [77,84].

6.2. The progress in the field of artificial inhibitors of MMP

Most research concentrates on treating diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR), since these conditions are connected with severe vision impairment. The most common therapeutic targets are already mentioned MMPs (MMP-2, MMP- 9) and VEGF, due to their crucial role in the development of retinopathy.

The first artificial inhibitors of matrix metalloproteinases were investigated for use in cancer therapy. Back in the 1990s, a link between tumor growth, angiogenesis and MMP activity was established. MMP inhibitors were deemed a potential breakthrough in cancer therapy-while most of drugs of that time were cytotoxic, targeting MMPs could potentially bypass defense mechanisms of cancer cells. Low bioavailability and harmful side effects soon dampened the early enthusiasm for treating cancer with such drugs, but research continued, often focusing on other diseases and next- generation inhibitors [81].

Then, in 2002 a novel, selective inhibitor of MMP-2 and MMP-9-Prinomastat/AG3340 was shown to significantly suppress oxygen-induced retinal neovascularization in an animal model. It has appeared to be a promising candidate for the treatment of neovascular retinal diseases, including diabetic retinopathy [85]. Such findings were certain to spur further research.

In 2007, Barnett et al. tested three different MMP inhibitors with various selectivities on animal model of oxygen- induced retinopathy: RO-31-9790 (broad spectrum inhibitor), AG3340 (MMP-2 and 9 selective) and DPC-A37668 (MMP-2 selective). While all drugs have been administered by intravitreous injection, AG3340 and DPC-A37668 were delivered orally and intraperitoneally as well. Intravitreal delivery resulted in noticeable reduction in neovascular area for all medicines tested, but only in case of RO-319790 the reduction has been significant. In the remaining drugs, the observed antiangiogenic effect might have been linked to healing of the wound caused by injection. DPC-A37668 did induce substantial reduction in neovascular area compared to the eyes of untreated animals, but it was really effective only with oral delivery. This makes DPC-A37668 the most promising out of all inhibitors tested, as it uses the least risky route of administration [22].

Bhatt and Addepalli considered if minocycline-induced MMP-2 and MMP-9 inhibition can be enhanced by aspirin, a non-selective COX inhibitor. Diabetic rats were treated with minocycline, aspirin, or both drugs. Individuals treated with both medicines showed far better retinal function than placebo-treated specimens, and resembled outcomes from nondiabetic control most closely [86].

6.3. The transcriptional regulators of MMP

Most of early research focused on inhibitors that bind in the MMP active site and chelate the zinc ion [81]. Nowadays, other, more sophisticated methods of regulating MMPs expression are studied as well.

In 2013, one research group tried to examine the effect of extracellular-signal-regulated kinases-1/2 (ERK1/2) inhibition on the expression of MMP-9 and TIMP-1 in the retinas of diabetic rats. The animals were divided in 3 groups: normal, STZ treated with no inhibitor injection and STZ with U0126 injection. Retinal tissue from animals treated with no inhibitor injection had significantly higher ERK1/2 activity and MMP-9 expression, along with the decreased expression of TIMP-1, compared to the control group. These changes were persistent over time. U0126 administration decreased ERK1/2 activity and MMP-9 expression markedly, simultaneously increasing TIMP-1 level. The findings from U0126-treated retinas resembled those from healthy rats [87].

On the other hand, Mishra and Kowluru investigated the influence of PARP-1 (poly(ADP ribose) polymerase-1) on transcription factors regulating *MMP-9* gene expression. PARP-1 binds with corresponding transcription factors and facilitates transcription. Its increased activity is correlated with elevated MMP-9 level and cellular damage. Control cells incubated in high glucose showed increased level of PARP-1 activity and MMP-9 expression, compared to normal glucose group. Such increase was not observed in cells with PARP-1 inhibitors incubated in high glucose. The results were confirmed in vivo in experiment on mice. This finding suggests the promising role of PARP-1 inhibitors in the treatment of DR [88].

6.4. The promise of plant-derived substances

Some natural and plant- derived substances are also being researched as prospective MMP inhibitors. Curcumin, a yellow pigment acquired from turmeric rhizome, was analyzed by Kumar et al. While its regulatory activity on various MMPs was demonstrated, it was non-specific and the bioavailability was poor. However, curcumin analogs, devised to be more selective and easily assimilable, could be important MMP inhibiting drugs in the future [89].

Another study used ethanol extract of *Dendrobium chrysotoxum* Lindl (DC), also known as fried-egg orchid. The tests on DC-treated diabetic rats showed decreased levels of VEGF, VEGF receptor 2, MMP 2 and 9,

compared to control group [90]. Chen et al. evaluated the effects of quercetin, a natural flavonoid, on the levels MMP-9 and VEGF in the serum. The research group consisted of STZ rats treated with quercetin, with non- treated diabetic and normal rats added as a control. The levels of MMP-9 and VEGF were reduced considerably in the quercetin group [91].

6.5. The growing potential of microRNA-based mechanisms

For many years gene therapy in DR promised enticing results to researchers. As our understanding of underlying genetic mechanisms and epigenetic modifications present in DR improves, various therapeutic approaches are investigated. Some novel strategies for the treatment of diabetic retinopathy concern microRNA targeting, a short non-coding RNA implicated in post-transcriptional regulation of gene expression [92]. It is vital to note that the content of serum microRNA-126 might serve as a marker in peripheral blood for early stages of PDR [93]. Wang et al. indicated a significant role of microRNA-365 (miRNA) in the pathogenesis of diabetic retinopathy by inhibiting TIMP-3, a protein known for its ability to inhibit VEGF-mediated angiogenesis [94,95].

Li et al. group was exploring potential of micro-RNA in DR treatment as well. They discovered that miRNA-200b might attenuate the development of diabetic retinopathy via down-regulating its target vascular endothelial growth factor A (VEGFA) gene [96]. It should be nonetheless noted that application of RNA as therapeutic tool is predominantly a matter of clinical trials.

6.6. Targeting epigenetic regulation of MMP gene expression

Kowluru et al. demonstrated that genes encoding MMP-9 and mitochondrial superoxide dismutase (SOD2) can undergo epigenetic modifications in the diabetic environment [8]. In the next study, they showed that DNA methylation plays a crucial role in regulating transcription of retinal MMP-9 in diabetes [97]. Their further research revealed that oxidative stress, elevated in diabetes, has the ability to modulate DNA methylation. As a result, regulation of oxidative stress by various means prevents the activation of retinal MMP-9, which might cease the development of diabetic retinopathy [31]. Certainly, better apprehension of these processes could provide us with entirely new ways of fighting diabetic retinopathy.

6.7. Anti-VEGF therapy as an alternative to panretinal laser photocoagulation

Apart from rapidly developing field of MMP inhibitors, a few other useful drugs emerged, including anti-VEGF medicines. They are used in DME therapy and have proved to be useful in complicated cases of PDR [98]. Some anti-VEGF drugs, like bevacizumab and ranibizumab, demonstrated visual improvement in DME treatment comparable to laser therapy [99]. Intravitreally administered ranibizumab appears to be good alternative for PRP (panretinal photocoagulation) in PDR treatment as well [100]. The downsides of anti-VEGF therapy include short duration of the effect, possible tractional retinal detachment and, rarely, endophthalmitis [101].

6.8. The use of mesenchymal stem cells in DR as a potential therapeutic tool

An interesting and atypical therapy uses mesenchymal stem cells. MSCs injection was found to discharge paracrine factors and differentiate into photoreceptor- and glial-like cells in the retinal tissue. The result was enhanced by integrity of the blood-retinal barrier, which helped to alleviate diabetic retinopathy in STZ rat model [102].

6.9. Can antihypertensive drugs help? The effects of candesartan and fenofibrate treatment on DR

Lastly, high glycaemia and elevated blood pressure are known risk factors for DR incidence and progression [103]. Therefore, drugs that are not designed for retinopathy treatment can also slow its progression, provided that they address metabolic problems associated with DR development. One study found beneficial influence of fenofibrate treatment in patients with type 2 diabetes. The incidence of DME or laser therapy (chosen endpoint of DR progression in research) in fenofibrate group was smaller than in placebo group, in patients with pre-existing retinopathy [104]. Another one considered effects of candesartan on retinopathy progression in type 2 diabetes. By the end of research, candesartan group seemed to shift towards milder retinopathy [105].

7. Final considerations

Due to the increase in life expectancy and high prevalence of DM, diabetic retinopathy states a great challenge to medicine worldwide. The described link between diabetic retinopathy and MMP activity points to potential treatment methods, which need further examination. Nevertheless, there are still many uncertainties in the field of specific relationships between MMP and TIMP, which need to be clarified before appropriate therapy is suggested.

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