

© Group of authors, 2023
UDC 616-092:577.15:616.36-004
DOI – <https://doi.org/10.14300/mnnc.2023.18052>
ISSN – 2073-8137

MATRIX METALLOPROTEINASES: THE ROLE IN EVOLUTION OF LIVER DISEASES

Koroy P. V., Dudov T. R., Yagoda A. V., Sarithala V. J.

Stavropol State Medical University, Russian Federation

МАТРИКСНЫЕ МЕТАЛЛОПРОТЕИНАЗЫ: РОЛЬ В ЭВОЛЮЦИИ ЗАБОЛЕВАНИЙ ПЕЧЕНИ

П. В. Корой, Т. Р. Дудов, А. В. Ягода, В. Д. Саритхала

Ставропольский государственный медицинский университет,
Российская Федерация

Chronic liver diseases are characterized by the activation of stellate cells and increased extracellular matrix (ECM) accumulation, which leads to the evolution and advancement of liver fibrosis. Hepatic fibrogenesis is based on an imbalance between the collection and degradation of ECM, caused, among other things, by impaired matrix metalloproteinases (MMPs) expression. The review presents data on the biological role of various MMPs in normal and liver diseases. Clarifying the place of MMP in noninvasive and early diagnosis of chronic liver diseases will optimize the management of this category of patients.

Keywords: matrix metalloproteinases, liver diseases, liver fibrosis

Хронические заболевания печени характеризуются активацией звездчатых клеток и повышенной аккумуляцией внеклеточного матрикса (ВКМ), что приводит к развитию и прогрессированию фиброза печени. В основе печеночного фиброгенеза лежит дисбаланс между накоплением и деградацией ВКМ, обусловленный, в том числе, нарушенной экспрессией матриксных металлопротеиназ (ММП). В обзоре представлены данные о биологической роли различных ММП в норме и при патологии печени. Уточнение места ММП в неинвазивной и ранней диагностике хронических заболеваний печени позволяет оптимизировать ведение данной категории больных.

Ключевые слова: матриксные металлопротеиназы, заболевания печени, фиброз печени

For citation: Koroy P. V., Dudov T. R., Yagoda A. V., Sarithala V. J. MATRIX METALLOPROTEINASES: THE ROLE IN EVOLUTION OF LIVER DISEASES. *Medical News of North Caucasus*. 2023;18(2):219-225.
DOI – <https://doi.org/10.14300/mnnc.2023.18052>

Для цитирования: Корой П. В., Дудов Т. Р., Ягода А. В., Саритхала В. Д. МАТРИКСНЫЕ МЕТАЛЛОПРОТЕИНАЗЫ: РОЛЬ В ЭВОЛЮЦИИ ЗАБОЛЕВАНИЙ ПЕЧЕНИ. *Медицинский вестник Северного Кавказа*. 2023;18(2):219-225.
DOI – <https://doi.org/10.14300/mnnc.2023.18052>

ECM – extracellular matrix
HBV – hepatitis B virus
HCC – hepatocellular carcinoma

HCV – hepatitis C virus
MMP – matrix metalloproteinase
TIMP – tissue inhibitor of matrix metalloproteinases

ECM consists of molecules necessary for intercellular interactions, cell adhesion, migration, proliferation, differentiation and survival. It supports the cellular infrastructure by creating mechanical scaffolds and is responsible for cell metabolism [1–3]. Cell-matrix interactions are carried out through a complex receptor system, including in conjunction with growth factors, cytokines, hormones, and other bioactive molecules [2].

The predominant structural components of liver ECM are collagen type I, III, V (interstitial proteins), type IV (in basement membranes), proteoglycans, laminin, fibronectin, etc. [1, 4]. Collagen fibers provide the basis for adhesion and restriction of cell movement. ECM proteins are found in Glisson's capsule, in the subendothelial space of Disse, periportally [1]. Excessive synthesis of ECM components (type I collagen, type III collagen, type IV collagen, fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans) leads to the evolution and advancement of liver fibrosis [5]. As a result

of ECM degradation, cells begin to migrate, which is one of the mechanisms accompanying tumour cell invasion.

A significant contribution in the regulation of the composition of liver ECM, both towards excessive synthesis (fibrogenesis) and towards noticeable degradation (fibrinolysis), is played by MMPs and their inhibitors, which use various substrates [6, 7]. In a normal liver, MMPs and their inhibitors are in dynamic balance, regulating the level of production of ECM components [5]. In activated stellate cells, the TIMP-1 expression is increased, which is aimed at inhibiting MMPs and accumulating ECM components. However, these same cells can conduce fibrosis regression through the liberation of degrading proteases [2, 8].

MMPs belong to a superfamily that includes four families: matrixins, astracins, bacterial serralisins, and adamalysins. MMPs or matrixins are calcium-dependent (zinc containing) endopeptidases that degrade components, regulate integrity and composition, and are involved in ECM signaling [2, 9, 10].

Almost all MMPs play a role in fibrosis, fibrinolysis, carcinogenesis, and liver regeneration [8]. In addition to ECM components (collagen, gelatin, elastin, and fibronectin), MMPs can cause cleavage of cell surface molecules and pericellular non-matrix proteins (leading to regulation of cell behavior), other regulatory molecules (serine protease inhibitors, cytokines, chemokines, adhesion molecules). They are involved in the implantation of trophoblast, embryogenesis, remodeling of bone, growth of neurons, wound healing, tissue regeneration, innate immune response and adaptive immune response, inflammation, and angiogenesis. Some MMPs have functions independent of catalytic activity: the hemopexin domain of MMP-12 has antimicrobial activity [11]. MMP-9 promotes HBV replication by suppressing the action of interferon- α [12] and activation of MMP-9 by β -estradiol and its extracellular space export leading to occludin cleavage, which suppresses the penetration and spread of HCV [13]. In general, MMPs regulate essential cellular processes like proliferation, differentiation, cellular migration, the process of adhesion, and cellular apoptosis, as well as influence gene expression and numerous aspects of inflammation [1, 2, 6, 8]. Due to their functions, MMPs and TIMPs play a crucial role in developing and advancing many inflammatory, autoimmune, fibrotic, oncological, and infectious diseases [2, 14].

To date, 28 MMPs have been discovered in vertebrates and 24 in humans. Human MMPs can be divided into six groups depending on substrate and structural specificity: collagenase group (MMP-1, MMP-8, MMP-13), stromelysin group (MMP-3, MMP-10, MMP-11, MMP-17), gelatinase group (MMP-2, MMP-9), matrilysin group (MMP-7, MMP-26), membrane MMPs group (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25), others MMPs (MMP-12, MMP-19, MMP-20, MMP-21, MMP-22, MMP-23, MMP-27, MMP-28). There are 24 genes encoding MMPs [1, 2, 7, 8, 15].

MMPs have a similar molecular structure, represented by several (5–6) domains:

- signal domain (N-terminal sequence) – a pre-domain of 18–20 amino acids, which is detached upon enzyme activation;
- a propeptide comprising about 80 amino acid residues, including a cysteine residue («cysteine switch») that interacts with the zinc ion of the catalytic domain (due to this, the enzyme is in an inactive (latent) state);
- the catalytic domain consists of about 170 amino acids, two zinc ions, and a minimum of one calcium ion. It coordinates the zinc ion by binding it to three histidine residues. The domain has a «methionine loop» of 8 methionine residues, which provides the correct spatial arrangement of the active center around the zinc ion;
- the linker loop domain or linker peptide (hinge region) is rich in proline, includes amino acid residues located in an arbitrary sequence, acts as a linking site between the catalytic and hemopexin-like domains;
- hemopexin domain contains about 200 amino acid residues and regulates specific interaction with the substrate and endogenous inhibitors [2, 3, 9, 16].

Based on structural diversity, several categories of MMPs are distinguished [2]:

- a) archetypal MMPs, including collagenase group (MMP-1, MMP-8, MMP-13), stromelysin group (MMP-3, MMP-10), and other MMPs (MMP-12, MMP-19, MMP-20, MMP-22, MMP-27). They contain a hemopexin domain, a catalytic domain, a hinge, an amino-terminal propeptide, and a signaling peptide inducing secretion from cells;
- b) gelatinases (MMP-2, MMP-9) resembling the structure of archetypal MMPs, containing a fibronectin domain;

c) matrilysins (MMP-7, MMP-26) are structurally similar to archetypal MMPs, but lack the domain of hemopexin;

d) secreted MMPs (MMP-11, MMP-21, MMP-28) contain a cleavable furin-like domain;

e) membrane MMPs (MMP-14, MMP-15, MMP-16, MMP-24) are localized on the cell surface and contain furin-like cleavage and transmembrane domains;

f) membrane MMPs (MMP-17, MMP-25) resemble archetypal MMPs and consist of a C-terminal glycosylphosphatidylinositol membrane anchor;

g) other MMPs (MMP-23A, MMP-23B) also resemble archetypal MMPs, do not have a hemopexin domain, contain the N-terminal domain of TM-II and the cytoplasmic C-terminal domain of the immunoglobulin-like adhesion molecule (Ig-CAM) [16, 17].

MMPs are produced as pre-proenzymes (MMP-11 and MMP-28 are secreted in the active form), which are activated in the non-proteolytic or proteolytic way in the extracellular space [7]. During translation, a signal peptide is removed from pre-pro-MMP to form pro-MMP. Then, under the influence of enzymes (serine proteases, endopeptidases, furin, plasmin, etc.), the «cysteine switch» is lysed. The propeptide is detached from the catalytic domain, which leads to the binding of the water molecule in the propeptide to the zinc ion, catalysis, and cleavage of the substrate, i.e., MMP is converted into an active form [2, 6, 8, 15, 16].

MMP activity and expression are regulated at various levels, such as gene transcription, activation, enzyme secretion, and the influence of endogenous inhibitors [6]. Regulation of MMP activity is a multilevel process. Its violation leads to a change in the structural and functional organization of tissues [1, 3, 9].

MMPs are produced by various types of cells, including fibroblasts, epithelial, endothelial, and inflammatory cells (neutrophils, monocytes, macrophages) [6, 16]. In the liver, all cells (hepatocytes, stellate cells, fibroblasts, sinusoidal endotheliocytes, hepatic macrophages (resident Kupffer cells, infiltrated macrophages), leukocytes) are capable of synthesizing MMPs; stellate cells are the primary producers [2, 9, 16].

Although MMPs are known for their antifibrotic effect due to the ability to destroy ECM proteins, under various pathological conditions, they can have a profibrotic impact by activating or inactivating cytokines, chemokines, growth factors, and adhesion molecules [6, 9, 16]. MMPs play a crucial role in ECM remodeling; however, disturbances in their expression and/or activity contribute to the advancement of liver diseases [2].

Several MMPs are involved in the initiation, advancement, and resolution of liver diseases, whose expression differs depending on acute liver injury, acute or chronic inflammation, liver fibrosis/cirrhosis, HCC, and metastasis of HCC. Few MMPs are involved in the regeneration of liver [1, 8, 18]:

- MMP-3, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13 and MMP-14 induce liver inflammation by participating in the release of cytokines that initiate infiltration and activation of macrophages and leukocytes;
- MMP-7, MMP-9, MMP-10, MMP-12, MMP-16 and MMP-19 are involved in the progression of fibrosis and ECM remodelling;
- MMP-1, MMP-2, MMP-8 and MMP-13 (indirectly MMP-10, MMP-24) are involved in liver fibrosis resolution by degradation of the ECM;
- MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-16 and MMP-28 are associated with HCC development;
- metastasis of HCC is a complex cascade of events consisting of endothelial-mesenchymal transition (MMP-3,

MMP-9, MMP-11, MMP-12), cellular invasion (MMP-2, MMP-3, MMP-8, MMP-9, MMP-10, MMP-13, MMP-14, MMP-16, MMP-28), angiogenesis (MMP-9, MMP-10), intravasation into the bloodstream (MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-14), extravasation to other tissues (MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-13, MMP-14, MMP-16, MMP-28).

MMPs are considered as «direct» (which reflects ECM turnover) and «indirect» (reflecting impaired liver function) biomarkers for diagnosing and determining the stage of liver fibrosis [2].

MMP-1 (collagenase-1, interstitial collagenase, fibroblast collagenase) plays a role in the regression of inflammation and fibrosis and promotes recovery and regeneration of the liver. It cleaves ECM substrates and other substrates such as collagen (types I and III); laminin; gelatin; complement C1q; interleukin-1 β ; and tumor necrosis factor- α . MMP-1 can activate MMP-2 and MMP-9. It is constitutively expressed in the normal liver; in pathological conditions, it is expressed by stellate and inflammatory cells (mast cells, Kupffer cells, monocytes) [2, 6, 18].

In chronic hepatitis C patients, the level of MMP-1 in the blood was negatively associated with the severity of the disease, and the combination of alpha-fetoprotein, collagen III/MMP-1 ratio, a ratio of aspartate aminotransferase/alanine aminotransferase and platelet count was significant in predicting the stage of fibrosis F2–F4 [19]. Increased MMP-1 expression in monocytes, Kupffer cells, and stellate cells was observed only in the early stages of non-alcoholic steatohepatitis, which indicates an inverse correlation of MMP-1 with hepatic fibrosis progression [20]. However, it is believed that MMP-1 enhances fibrosis in non-alcoholic steatohepatitis [6]. In chronic hepatitis C patients and patients with non-alcoholic steatohepatitis, blood levels of MMP-1 were associated with early fibrosis (necro- and fibro-inflammation). At the same time, such a relationship was absent in the late fibrosis stages [20]. There were no differences in MMP-1 activity in alcoholic liver disease patients depending on the existence or non-existence of cirrhosis [21].

In models of liver fibrosis, hyperexpression of MMP-1 led to a reduction in fibrosis, promoted the degradation of ECM (collagen types I and III), an induced proliferation of hepatocytes and regeneration of the liver, and apoptosis of stellate cells [2, 8, 22]. The imbalance between MMP-1 and TIMP-1 in favor of the prevalence of the latter is an essential mechanism of liver fibrosis [22].

Intravenous administration of pro-MMP-1 within the adenoviral vector (Ad5MMP-1) reduced liver fibrosis in rats, accompanied by an increase in the expression of MMP-1 and its activity in the liver. ECM degradation against this background was accompanied by repression, dissolution, and/or apoptosis of the activated stellate cells. This led to a drop in TIMP expression and an increase in hepatocyte proliferation (liver regeneration) [2]. Transplantation of stem cells of bone marrow containing an adenoviral vector with MMP-1 induced the synthesis of MMP-1 (and MMP-14), reduced the collagen levels, and attenuated the stellate cell activation, resulting in a reduction in liver damage and fibrosis [22, 23].

Allelic polymorphism of MMP-1 is involved in HCC development [24].

MMP-2 (gelatinase A) is localized in vascular areas and is involved in maintaining vascular homeostasis and remodeling the ECM of the liver [1, 6]. It is expressed by numerous liver cells, more often by stellate and Kupffer cells. It is secreted as a proenzyme activated by MMP-1 and MMP-14 [2, 6]. Unlike collagenases, gelatinases (MMP-2 and MMP-9) are involved in the binding and cleavage of denatured tropocollagen, which suggests a consistent

and synergistic behavior of collagenases and gelatinases during the degradation of collagen [25]. MMP-2 induces the production of reactive oxygen species and can cause inflammation [2]. MMP-2 activity is inversely proportional to the activity of MMP-9 [6].

In alcoholic liver disease patients, the content of MMP-2 in the blood increases at all stages of cirrhosis, while the MMP-8 and MMP-9 levels are grown only in severe cirrhosis (stage C) [26].

MMP-2 is involved in both progression and regression of fibrosis [2, 6]. Regardless of etiology (in the absence of expression in the normal liver), a correlation of MMP-2 expression with the progression of fibrosis was found, which indicates a profibrogenic potential [2]. Increased MMP-2 expression was connected with chronic hepatitis, ischemia-reperfusion injury, alcoholic cirrhosis, biliary atresia, and HCC [26]. Increased expression and activity in hepatocytes of MMP-2 positively correlated with the severity of fibrosis [27]. Elevated levels of inflammatory mediators (interleukin-1) enhance the synthesis of MMPs and their secretion, including that of MMP-2. In contrast, the activated MMPs are involved in the degradation and negative regulation of the activity interleukin-1 [2].

MMP-2 suppresses the expression of type I collagen activated by stellate cells; its absence contributes to increased liver fibrosis [8]. Thus, in mice with MMP-2 deficiency, an increased fibrotic profile was observed, as well as the acceleration of fibrosis induced by toxins and cholestasis [2]. MMP-2 mRNA expression was increased at all fibrosis stages, but active MMP-2 was found in later stages (during fibrosis resolution), indicating its role in liver damage resolution [28].

In vitro, delivery of MMP-2 RNA coupled with vitamin A to stellate cells inhibited the activation and proliferation of stellate cells and reduced the deposition of collagen I [29]. Rosmarinic acid returned activated stellate cells to the resting phenotype, inhibited MMP-2 activity, and suppressed reactive oxygen species, lipid peroxidation, and oxidative stress [30].

MMP-3 (stromelysin-1) is produced as pro-MMP-3 and is activated by serine proteases. Regulates remodeling of ECM, having the ability to cleave proteoglycans, fibronectin, laminin, gelatin, elastin, and various types of collagens, and also activates other MMPs (MMP-1, -7, -9) [2]. MMP-3 is involved in the early stages of fibrosis during inflammation; therefore, it is expressed not only by stellate cells but also by infiltrated macrophages [2, 6].

Increased MMP-3 expression was observed in liver inflammation caused by ischemia-reperfusion injury, HCC (and metastasis). A decrease in the expression of MMP-3 by stellate cells and macrophages was observed during fibrosis resolution [2]. MMP-3 expression also regulated the induction of liver cirrhosis in rats [6].

MMP-3 is involved in hepatocyte growth factor-induced cell invasion and metastasis of HCC, with higher levels of expression observed in tumour cells and around blood vessels. MMP-3 polymorphism has been associated with fibrosis progression and poor HCC prognosis [2, 6, 8].

MMP-7 (matrilysin-7) is secreted by bile duct epithelial cells, Kupffer cells, and periportal hepatocytes and is associated with tissue remodeling in liver fibrosis, including that due to biliary atresia [2, 6, 31]. In the normal liver, MMP-7 expression is practically absent [8]. Increased MMP-7 expression in the epithelium of biliary tract and periportal hepatocytes positively correlated with blood levels of MMP-7 and liver fibrosis associated with biliary atresia [32]. It is assumed that MMP-7 is a prognostic marker of biliary atresia [33, 34].

MMP-7 expression was increased in many types of cancer, such as breast, lung, prostate, and ovarian cancer,

and benign and malignant colorectal tumours [6]. It has the maximum ability to destroy elastin, which is contained in the blood vessels' basement membrane, which implies the potential for metastasis to the portal vein through a hematogenous way [2]. The expression of MMP-7 produced by tumour cells (including the activity of mRNA, protein and enzyme) was noticed in patients with liver metastases of colorectal carcinoma. However, there is no information on the hyperexpression of MMP-7 in liver tissue in HCC [8].

In addition, MMP-7 is expressed by liver progenitor cells and is associated with regulating regeneration in liver damage [2].

MMP-8 (collagenase-2), synthesized by neutrophils and macrophages, is involved in fibrosis resolution through the destruction of collagen and the control of inflammation by breaking down cytokines and chemokines [35]. Infiltrated neutrophils are accountable for the expression of MMP-8 during recovery after cholestatic liver injury [8]. However, in acute hepatitis in mice induced by tumour necrosis factor- α , deficiency of MMP-8 disrupted leukocyte migration and chemokine release, indicating MMP-8 positive role in the regulation of acute inflammation [2, 6]. MMP-8 expression was associated with increased expression of hepatocyte growth factor and proliferation of hepatocytes [35], as well as with a decrease in the severity of liver fibrosis [8]. On the other hand, MMP-8 released by macrophages can activate stellate and myofibroblast-like cells, which leads to liver fibrosis [6, 36].

MMP-8 content and its activity in the blood (along with MMP-2 and -9) increased in alcoholic liver cirrhosis, reaching maximum values in class C cases [26]. MMP-8 is also involved in HCC, promoting the invasion and migration of tumour cells [37].

Adenovirus-mediated hyperexpression of MMP-8 induced resolution of fibrosis in various models [38]. In vivo administration of an adenoviral vector with MMP-8 (AdMMP-8) in a model of liver cirrhosis in rats led to the expression of pro-MMP-8 in the liver and its active form, reversal of fibrosis, improvement of functional tests of the liver and intrahepatic blood pressure, decrease in the expression of transforming growth factor- β mRNA and a significant increase in MMP-9 expression and hepatocyte growth factor [2]. Administration of the cMMP-8-1K1 protein containing MMP-8 and hepatocyte growth factor promoted the proliferation of hepatocytes and liver regeneration, reduced fibrosis, and protected the liver function post hepatectomy [38].

MMP-9 (Gelatinase-B) is secreted by neutrophils, macrophages, fibroblasts, and endothelial cells, which can degrade ECM, including collagen type IV, elastin, and fibronectin. Fibronectin interaction with integrin $\alpha 4 \beta 1$ enhances MMP-9 expression and activity during ischemia-reperfusion injury [2, 6, 8]. MMP-9 is involved in ECM degradation and increases the permeability of matrix and leukocyte extravasation, intensifying infiltration of leukocytes and inflammation and impairing the function of liver and its regeneration during ischemia-reperfusion injury [1].

Expression of MMP-9 is activated in chronic hepatitis B patients, and HBV induces the production MMP-9 in mononuclear cells and macrophages in peripheral blood [8]. MMP-9 content and its activity in the blood were increased in patients with class C of alcoholic liver cirrhosis [26]. Increased expression and activity of MMP-9 in hepatocytes positively correlated with the severity of fibrosis [27]. Patients with chronic hepatitis C had high levels of MMP-9 and increased TIMP-1 in the blood, coupled with the severity of fibrosis; according to the authors, the MMP-9/TIMP-1 complex is a marker of active fibrogenesis [39].

MMP-9 inhibition is a promising approach in the treatment of ischemia-reperfusion injury: 1) deficiency

or administration of MMP-9 inhibitors reduced infiltration of leukocytes, inflammation of the liver and its damage; 2) decreased nitric oxide release induced by nitric oxide synthase, reduced MMP-9 expression, reduced inflammation, and liver damage; 3) selective inhibition of MMP-9 prevented the cleavage of vascular endothelial growth factor, which increased the recruitment of progenitors of sinusoidal endothelial cells and accelerated liver regeneration [2, 28, 40].

MMP-9 has a dual role in fibrogenesis. Thus, MMP-9 induces apoptosis of stellate cells via the $\alpha 5 \beta 1$ integrin. Proteolytically inactive MMP-9 mutants bound to TIMP-1 attenuated CCl₄-induced fibrosis. This was confirmed by a decrease in the portal and periportal collagen deposition, inhibition of the expression of fibrogenesis marker genes, suppression of differentiation, and increased apoptosis of stellate cells [2, 8]. The fibrinolytic role of MMP-9 produced by Kupffer cells was demonstrated in a study by M. Feng et al. [41]. Interestingly, MMP-9 activity is modulated by matrix rigidity: fibrous ECM suppresses the expression of MMP-9, secretion, and action in liver fibrosis (and HCC) [42]. On the contrary, myofibroblast-like cells of fibrous tissue increase MMP-2, MMP-9, and TIMP expression, with subsequent accumulation of collagen I and III [8]. Evidence shows that inhibition of MMP-9 attenuates fibrogenesis and promotes liver fibrosis resolution [2].

Increased MMP-9 expression is associated with poor prognosis of HCC, as evidenced by correlation with capsule infiltration, number of nodules, size of the tumour and differentiation, vascular invasion, prediction of recurrence, and survival after tumour resection. MMP-9 degrades collagen IV (basement membrane structural component) and plays a role in neoangiogenesis, leading to invasion and metastasis. NO, secreted by the cancer cells, modulates the production of MMP-9, promoting angiogenesis, invasion, and metastasis of HCC. Thus, MMP-9 is a marker of the prognosis of HCC [2, 8].

MMP-9 expression is increased in acute and fulminant liver failure, promoting extravasation and cerebral edema due to integral loss of the blood-brain barrier. MMP-9 depletion or its inhibition increases a patient's survival, improved liver function, and brain damage in the early stages of the process [43].

MMP-10 (stromelysin-2) is produced by parenchymal and non-parenchymal liver cells, has a wide range of substrates, including ECM components, activates MMP-1, MMP-7, MMP-8, MMP-9, and MMP-13. Expression of MMP-10 is increased in acute liver injury, liver cirrhosis, and HCC [1]. MMP-10 promotes recovery and regeneration of liver tissue following partial hepatectomy and ligation of the bile duct [44], as well as HCC progression and metastasis through the CXC chemokine receptor-4/stromal factor-1 (CXCR4/SDF1) axis [45].

MMP-11 (stromelysin-3) is associated with HCC and controls its miR-125a-regulated proliferation and metastasis. Several variants of the MMP-11 gene are associated with the early stage of carcinoma and can be a useful biomarker in carcinoma [46]. Also, there is protective action of MMP-11 against diabetes, obesity, and steatohepatitis by regulating energy metabolism and intensifying fat mobilization and its metabolism [47]. In ischemia-reperfusion injury, MMP-11 expression increases; and may play a role in liver regeneration [2].

MMP-12 (matrilysin) is produced by macrophages and is activated in diseases like schistosomiasis and cirrhosis of the liver [8]. In HCC, overexpression of MMP-12 correlated with tumour size, α -fetoprotein, and poor survival [2]. MMP-12 expression is increased after 24 hours of ischemia-reperfusion injury and plays a part in macrophage-mediated degradation of ECM and wound healing [6].

MMP-12 is involved in the destruction of elastin. Suppression of its activity led to excessive accumulation of elastin and fibrosis progression [8]. On the other hand, MMP-12 inhibits MMPs which degrades ECM (MMP-2, MMP-9, MMP-13), exacerbating interleukin-13-dependent liver fibrosis [2, 6]. MMP-12 expression is closely associated with the evolution of Th2-dependent fibrosis [8].

MMP-13 (collagenase-3) is expressed in acute liver injury and plays a role in the proliferation and repair of hepatocytes, inducing hepatic growth factor, and in MMP-2 and MMP-9 expression [2, 6]. MMP-13, produced by macrophages and Kupffer cells, is associated with the resolution of liver fibrosis [27].

On the contrary, it is assumed that MMP-13 plays a significant role in hepatic fibrogenesis, as it activates transforming growth factor- β 1, a key cytokine in developing fibrosis [8]. It has been demonstrated that the loss of MMP-13 is accompanied by the inhibition of stellate cell activation and proliferation and improves cholestasis-induced liver damage and fibrosis [2, 8]. A point of view is expressed that collagen degradation changes intercellular and cell-matrix interactions, which leads to necrosis and apoptosis of hepatocytes, the release of cytokines, and increased leukocyte infiltration and inflammation. Studies have shown that ECM degradation at an early stage of fibrosis induces the proliferation and differentiation of stellate cells into myofibroblast-like cells, and MMP-13 mediated breakdown of connective tissue growth factor causes an acute inflammatory response [48]. MMP-13 also promotes pro-inflammatory mediators' expression (tumour necrosis factor- α , CCL2), which modulates initial liver damage.

The levels of MMP-13 in the blood are increased in alcoholic liver cirrhosis patients, which was regarded as its diagnostic marker [21, 49]. Increased MMP-13 expression and activity in hepatocytes positively correlated with the severity of fibrosis [27]. In HCC, increased levels of MMP-13 are positively associated with the progression and early metastasis of HCC [50, 51].

MMP-14 (MT1-MMP) consists of a chain of hydrophobic amino acids that attaches the molecule to the membrane of leukocytes and macrophages [52]. MMP-14 persists during the early resolution of liver fibrosis and contributes to fibrinolysis. It degrades adhesion molecules, fibronectin, activates MMP-2 and MMP-13 and enhances the recruitment of leukocytes and macrophages during ischemia-reperfusion injury [8].

Increased MMP-14 expression and activity in hepatocytes positively correlate with the severity of fibrosis [27]. MMP-14 is expressed highly in the tissue of HCC compared to non-tumour tissue and is associated with invasion of tissue, metastasis, and tumour recurrence [6].

MMP-15 (MT2-MMP) activates MMP-2 and MMP-13, thereby changing the integrity of the ECM. The expression of MMP-15 is suppressed during liver regeneration after partial hepatectomy [2, 8]. Indirectly involved in the invasion of HCC cells [53].

MMP-16 (MT3-MMP) is located on fibroblasts' surface, can destroy ECM components (collagen), and can activate MMP-2. MMP-16 is expressed in hepatitis, liver cirrhosis, and HCC. MMP-16 supports the invasion

and metastasis of tumour cells; therefore, it has been proposed as a prognostic marker of HCC [6, 54].

Expressed MMP-19 (MMP-RASI-1) in the liver is associated with fibrosis in the initial stages of damage and has an antifibrotic effect in the later stages. At the onset of injury, MMP-19 deficiency improves liver fibrosis by reducing fibrous deposits associated with changes in signaling pathways of transforming factor- β 1 and insulin-like growth factor-1 [8]. In mice deficient in MMP-19, a decrease in liver fibrosis was observed due to a reduction in ECM remodeling and accelerated regeneration [2, 6].

MMP-23 contains an N-terminal transmembrane domain-II for attaching the protein to the cell surface and a C-terminal domain of an immunoglobulin-like cell adhesion molecule (Ig-CAM) for mediating protein-to-protein and protein-lipid interactions. MMP-23 also contains a small toxin-like domain (TxD) that regulates intracellular potassium channel transport and controls cellular functions. Hypermethylated MMP-23 is activated in the HCC model and is involved in long-term hepatocarcinogenesis [55]. In addition, MMP-23b promotes the regeneration of liver and proliferation of hepatocytes mediated by tumour necrosis factor- α [6].

MMP-24 (MT5-MMP) mediates N-cadherin (CDH2) cleavage and intercellular interactions. Its increased activity was noticed in the regenerating liver [2, 8].

MMP-25 (MT6-MMP) contains a glycosylphosphatidylinositol anchor for attachment to the plasma membrane. It is involved in tumour invasion and metastasis through MMP activation and the nuclear factor- κ B signaling pathway [56]. In response to inflammation, MMP-25 weakens the action of the alpha-1 proteinase inhibitor, the primary tissue protector from proteolytic enzymes of neutrophils, which facilitates the transendothelial migration of neutrophils to inflammation sites [2].

MMP-28 (epilisin) increases with alcohol-mediated damage to hepatocytes and the progression of inflammation [6]. In HCC, increased MMP-28 activity was observed, which induces migration and invasion and is associated with a poor prognosis [57].

Although MMPs are promising therapeutic targets for liver pathology, it must be remembered that: 1) ECM fragments resulting from its degradation are biologically active and can mediate secondary effects affecting physiological and pathological processes; 2) MMPs are associated with normal physiological processes, including ovulation, trophoblast invasion, embryonic development; 3) they play a role in immune processes, activate and inhibit cytokines and chemokines; 4) increased expression and activity of MMPs are associated with the development and metastasis of cancer; 5) their use is limited by poor specificity, selectivity, bioavailability, pharmacokinetics, side effects, and toxicity; 6) dysregulation of MMPs alters ECM homeostasis, contributing to aging and neurodegenerative disorders [58, 59].

Conclusion. Thus, MMPs play an essential biological role in the body and can be new diagnostic markers and promising therapeutic targets for liver pathology. However, to date, their role as biomarkers, as well as the role of MMP genetic polymorphisms as risk factors for chronic liver diseases, including HCC, has not been determined. Clarifying the possibilities of MMPs use in non-invasive and early diagnosis of chronic liver diseases will optimize the management of this category of patients.

Disclosures: The authors declare no conflict of interest.

References

1. Duarte S., Baber J., Fujii T., Coito A. J. Matrix metalloproteinases in liver injury, repair and fibrosis. *Matrix Biol.* 2015;44:46:147-156. <https://doi.org/10.1016/j.matbio.2015.01.004>
2. Geervliet E., Bansal R. Matrix metalloproteinases as potential biomarkers and therapeutic targets in liver diseases. *Cells.* 2020;9(5):1212. <https://doi.org/10.3390/cells9051212>

3. Jabłońska-Trypuć A., Matejczyk M., Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. *J. Enzyme Inhib. Med. Chem.* 2016;3(1):177-183. <https://doi.org/10.3109/14756366.2016.1161620>
4. Arteel G. E., Naba A. The liver matrixome – looking beyond collagens. *JHEP Reports.* 2020;2(4):100115. <https://doi.org/10.1016/j.jhepr.2020.100115>
5. Chen G., Xia B., Fu Q., Huang X., Wang F. [et al.] Matrix mechanics as regulatory factors and therapeutic targets in hepatic fibrosis. *Int. J. Biol. Sci.* 2019;15(12):2509-2521. <https://doi.org/10.7150/ijbs.37500>
6. Naim A., Pan Q., Baig M. S. Matrix metalloproteinases (MMPs) in liver diseases. *J. Clin. Exp. Hepatol.* 2017;7(4):367-372. <https://doi.org/10.1016/j.jceh.2017.09.004>
7. Robert S., Gicquel T., Bodin A., Lagente V., Boichot E. Characterization of the MMP/TIMP imbalance and collagen production induced by IL-1 β or TNF- α release from human hepatic stellate cells. *PLoS One.* 2016;11(4):e0153118. <https://doi.org/10.1371/journal.pone.0153118>
8. Roeb E. Matrix metalloproteinases and liver fibrosis (translational aspects). *Matrix Biol.* 2018;68-69:463-473. <https://doi.org/10.1016/j.matbio.2017.12.012>
9. Shadrina A. S., Plieva Ya. Z., Kushlinskii D. N., Morozov A. A., Filipenko M. L. [et al.] Classification, regulation of activity, genetic polymorphism of matrix metalloproteinases in normal and pathological conditions. *Al'manah klinicheskoy mediciny. – Almanac of Clinical Medicine.* 2017;45(4):266-279. <https://doi.org/10.18786/2072-0505-2017-45-4-266-279>
10. Binder M. J., McCoombe S., Williams E. D., McCulloch D., Ward A. The extracellular matrix in cancer progression: Role of hyalactan proteoglycans and ADAMTS enzymes. *Cancer Lett.* 2017;385:55-64. <https://doi.org/10.1016/j.canlet.2016.11.001>
11. Apte S. S., Parks W. C. Metalloproteinases: a parade of functions in matrix biology and an outlook for the future. *Matrix Biology.* 2015;44-46:1-6. <https://doi.org/10.1016/j.matbio.2015.04.005>
12. Chen J., Xu W., Chen Y., Xie X., Zhang Y. [et al.] Matrix metalloproteinase 9 facilitates hepatitis B virus replication through binding with type I interferon (IFN) receptor 1 to repress IFN/JAK/STAT signaling. *Virology.* 2017;91(8):e01824-16. <https://doi.org/10.1128/JVI.01824-16>
13. Ulitzky L., Lafer M. M., KuKuruga M. A., Silberstein E., Cehan N., Taylor D. R. A new signaling pathway for HCV inhibition by estrogen: GPR30 activation leads to cleavage of occludin by MMP-9. *PLoS One.* 2016;11(1):e0145212. <https://doi.org/10.1371/journal.pone.0145212>
14. Chuang H.-M., Chen Y.-S., Harn H.-J. The Versatile role of matrix metalloproteinase for the diverse results of fibrosis treatment. *Molecules.* 2019;24(22):4188. <https://doi.org/10.3390/molecules24224188>
15. Grigorkevich O. S., Mokrov G. V., Kosova L. Yu. Matrix metalloproteinases and their inhibitors. *Farmakokinetika i farmakodinamika. – Pharmacokinetics and pharmacodynamics.* 2019;2:3-16. <https://doi.org/10.24411/2587-7836-2019-10040>
16. Cui N., Hu M., Khalil R. A. Biochemical and biological attributes of matrix metalloproteinases. *Prog. Mol. Biol. Transl. Sci.* 2017;147:1-73. <https://doi.org/10.1016/bs.pmbts.2017.02.005>
17. Madzharova E., Kastl P., Sabino F., Keller U. A. D. Post-translational modification-dependent activity of matrix metalloproteinases. *Int. J. Mol. Sci.* 2019;20(12):3077. <https://doi.org/10.3390/ijms20123077>
18. Roderfeld M. Matrix metalloproteinase functions in hepatic injury and fibrosis. *Matrix Biol.* 2018;68-69:452-462. <https://doi.org/10.1016/j.matbio.2017.11.011>
19. Attallah A., El-Far M., Malak C. A. A., Omeran M. M., Farid K. [et al.] Fibro-check: A combination of direct and indirect markers for liver fibrosis staging in chronic hepatitis C patients. *Ann. Hepatol.* 2015;14(2):225-233.
20. Ando W., Yokomori H., Tsutsui N., Yamanouchi E., Suzuki Y. [et al.] Serum matrix metalloproteinase-1 level represents disease activity as opposed to fibrosis in patients with histologically proven nonalcoholic steatohepatitis. *Clin. Mol. Hepatol.* 2018;24(1):61-76. <https://doi.org/10.3350/cmh.2017.0030>
21. Prystupa A., Szpetnar M., Boguszewska-Czubara A., Grzybowski A., Sak J. [et al.] Activity of MMP1 and MMP13 and amino acid metabolism in patients with alcoholic liver cirrhosis. *Medical Science Monitor.* 2015;21:1008-1014. <https://doi.org/10.12659/MSM.892312>
22. Moskalenko M. I., Ponomarenko I. V., Polonikov A. V., Churnosov M. I. Polymorphic locus RS17577 of MMP9 gene is associated with essential hypertension in men. *Medical News of North Caucasus.* 2020;15(1):39-43. <https://doi.org/10.14300/mnnc.2020.15008>
23. Itaba N., Kono Y., Watanabe K., Yokobata T., Oka H. [et al.] Reversal of established liver fibrosis by IC-2-engineered mesenchymal stem cell sheets. *Sci. Rep.* 2019;9(1):6841. <https://doi.org/10.1038/s41598-019-43298-0>
24. Zhou Z., Ma X., Wang F.-M., Sun L., Zhang G. A Matrix metalloproteinase-1 polymorphism, MMP1-1607 (1G>2G), is associated with increased cancer risk: a meta-analysis including 21,327 patients. *Dis. Markers.* 2018;2018:7565834. <https://doi.org/10.1155/2018/7565834>
25. Powell B., Malaspina D. C., Szleifer I., Dhaher Y. Effect of collagenase-gelatinase ratio on the mechanical properties of a collagen fibril: a combined Monte Carlo-molecular dynamics study. *Biomech. Model. Mechanobiol.* 2019;18(6):1809-1819. <https://doi.org/10.1007/s10237-019-01178-6>
26. Prystupa A., Boguszewska-Czubara A., Bojarska-Junak A., Toruń-Jurkowska A., Roliński J. [et al.] Activity of MMP-2, MMP-8 and MMP-9 in serum as a marker of progression of alcoholic liver disease in people from Lublin Region, eastern Poland. *Ann. Agric. Environ. Med.* 2015;22(2):325-328. <https://doi.org/10.5604/12321966.1152088>
27. Calabro S. R., Maczurek A. E., Morgan A. J., Tu T., Wen V. W. [et al.] Hepatocyte produced matrix metalloproteinases are regulated by CD147 in liver fibrogenesis. *PLoS ONE.* 2014;9(7):e90571. <https://doi.org/10.1371/journal.pone.0090571>
28. Kato H., Kuriyama N., Duarte S., Clavien P.-A., Busutil R. W. [et al.] MMP-9 deficiency shelters endothelial PECAM-1 expression and enhances regeneration of steatotic livers after ischemia and reperfusion injury. *J. Hepatol.* 2014;60(5):1032-1039. <https://doi.org/10.1016/j.jhep.2013.12.022>
29. Li Y., Liu F., Ding F., Chen P., Tang M. Inhibition of liver fibrosis using vitamin A-coupled liposomes to deliver matrix metalloproteinase-2 siRNA in vitro. *Mol. Med. Rep.* 2015;12(3):3453-3461. <https://doi.org/10.3892/mmr.2015.3842>
30. Lu C., Zou Y., Liu Y., Niu Y. Rosmarinic acid counteracts activation of hepatic stellate cells via inhibiting the ROS-dependent MMP-2 activity: involvement of Nrf2 antioxidant system. *Toxicol. Appl. Pharmacol.* 2017;318:69-78. <https://doi.org/10.1016/j.taap.2017.01.008>
31. Irvine K. M., Wockner L. F., Hoffmann I., Horsfall L. U., Fagan K. J. [et al.] Multiplex serum protein analysis identifies novel biomarkers of advanced fibrosis in patients with chronic liver disease with the potential to improve diagnostic accuracy of established biomarkers. *PLoS One.* 2016;11(11):e0167001. <https://doi.org/10.1371/journal.pone.0167001>
32. Kerola A., Lampela H., Lohi J., Heikkilä P., Mutanen A. [et al.] Increased MMP-7 expression in biliary epithelium and serum underpins native liver fibrosis after successful portoenterostomy in biliary atresia. *J. Pathol. Clin. Res.* 2016;2(3):187-198. <https://doi.org/10.1002/cjp2.50>
33. Harpavat S. MMP-7: the next best serum biomarker for biliary atresia? *J. Pediatr.* 2019;208:8-9. <https://doi.org/10.1016/j.jpeds.2019.01.026>
34. Wu J.-F., Jeng Y.-M., Chen H.-L., Ni Y.-H., Hsu H.-Y. [et al.] Quantification of serum matrix metalloproteinase 7 levels may assist in the diagnosis and predict the outcome for patients with biliary atresia. *J. Pediatr.* 2019;208:30-37.e1. <https://doi.org/10.1016/j.jpeds.2018.12.006>
35. Giannandrea M., Parks W. C. Diverse functions of matrix metalloproteinases during fibrosis. *Dis. Model. Mech.* 2014;7(2):193-203. <https://doi.org/10.1242/dmm.012062>
36. Baig M. S., Yaqoob U., Cao S., Saqib U., Shah V. H. Non-canonical role of matrix metalloproteinase (MMP) in activation and migration of hepatic stellate cells (HSCs). *Life Sci.* 2016;155:155-160. <https://doi.org/10.1016/j.lfs.2016.04.031>
37. Qin G., Luo M., Chen J., Dang Y., Chen G. [et al.] Reciprocal activation between MMP-8 and TGF-1 stimulates

- EMT and malignant progression of hepatocellular carcinoma. *Cancer Lett.* 2016;374(1):85-95. <https://doi.org/10.1016/j.canlet.2016.02.001>
38. Liu J., Li J., Fu W., Tang J., Feng X. [et al.] Adenoviral delivery of truncated MMP-8 fused with the hepatocyte growth factor mutant 1K1 ameliorates liver cirrhosis and promotes hepatocyte proliferation. *Drug Des. Dev. Ther.* 2015;9:5655-5667. <https://doi.org/10.2147/DDDT.S92481>
39. Medeiros T., Saraiva G. N., Moraes L. A., Gomes A. C., Lacerda G. S. [et al.] Liver fibrosis improvement in chronic hepatitis C after direct acting-antivirals is accompanied by reduced profibrogenic biomarkers-a role for MMP-9/TIMP-1. *Dig. Liver Dis.* 2020;52(10):1170-1177. <https://doi.org/10.1016/j.dld.2020.05.004>
40. Wang X., Maretti-Mira A. C., Wang L., Deleve L. D. Liver-selective MMP-9 inhibition in the rat eliminates ischemia-reperfusion injury and accelerates liver regeneration. *Hepatology.* 2019;69(1):314-328. <https://doi.org/10.1002/hep.30169>
41. Feng M., Ding J., Wang M., Zhang J., Zhu X. [et al.] Kupfer-derived matrix metalloproteinase-9 contributes to liver fibrosis resolution. *Int. J. Biol. Sci.* 2018;14(9):1033-1040. <https://doi.org/10.7150/ijbs.25589>
42. Lachowski D., Cortes E., Rice A., Pinato D., Rombouts K. [et al.] Matrix stiffness modulates the activity of MMP-9 and TIMP-1 in hepatic stellate cells to perpetuate fibrosis. *Sci. Rep.* 2019;9(1):7299. <https://doi.org/10.1038/s41598-019-43759-6>
43. Hori T., Uemoto S., Walden L.B., Chen F., Baine A.-M. T. [et al.] Matrix metalloproteinase-9 as a therapeutic target for the progression of fulminant liver failure with hepatic encephalopathy: a pilot study in mice. *Hepatol. Res.* 2014;44(6):651-662. <https://doi.org/10.1111/hepr.12161>
44. Garcia-Irigoyen O., Carotti S., Latasa M. U., Uriarte I., Fernandez-Barrena M. G. [et al.] A. Matrix metalloproteinase-10 expression is induced during hepatic injury and plays a fundamental role in liver tissue repair. *Liver Int.* 2014;34(7):e257-e270. <https://doi.org/10.1111/liv.12337>
45. Garcia-Irigoyen O., Latasa M. U., Carotti S., Uriarte I., Elizalde M. [et al.] Matrix metalloproteinase 10 contributes to hepatocarcinogenesis in a novel crosstalk with the stromal derived factor 1/C-X-C chemokine receptor 4 axis. *Hepatology.* 2015;62(1):166-178. <https://doi.org/10.1002/hep.27798>
46. Wang B., Hsu C.-J., Lee H.-L., Chou C.-H., Su C.-M. [et al.] Impact of matrix metalloproteinase-11 gene polymorphisms upon the development and progression of hepatocellular carcinoma. *Int. J. Med. Sci.* 2018;15(6):653-658. <https://doi.org/10.7150/ijms.23733>
47. Dali-Youcef N., Hnia K., Blaise S., Messaddeq N., Blanc S. [et al.] Matrix metalloproteinase 11 protects from diabetes and promotes metabolic switch. *Sci. Rep.* 2016;6:25140. <https://doi.org/10.1038/srep25140>
48. George J., Tsutsumi M., Tsuchishima M. MMP-13 deletion decreases profibrogenic molecules and attenuates N-nitrosodimethylamine-induced liver injury and fibrosis in mice. *J. Cell. Mol. Med.* 2017;21(12):3821-3835. <https://doi.org/10.1111/jcmm.13304>
49. Zaluska W., Prystupa A., Szpetnar M., Boguszewska-Czubara A., Grzybowski A., Sak J. Activity of MMP1 and MMP13 and amino acid metabolism in patients with alcoholic liver cirrhosis. *Med Sci. Monit.* 2015;21:1008-1014. <https://doi.org/10.12659/MSM.892312>
50. Jin D., Tao J., Li D., Wang Y., Li L. [et al.] Golgi protein 73 activation of MMP-13 promotes hepatocellular carcinoma cell invasion. *Oncotarget.* 2015;6(32):33523-33533. <https://doi.org/10.18632/oncotarget.5590>
51. Zhang H. A., Yan H. Q., Wang F., Wang Y. Y., Jiang Y. N. [et al.] TIPE2 inhibits TNF- α -induced hepatocellular carcinoma cell metastasis via Erk1/2 downregulation and NF- κ B activation. *Int. J. Oncol.* 2015;46(1):254-264. <https://doi.org/10.3892/ijo.2014.2725>
52. Itoh Y. Membrane-type matrix metalloproteinases: their functions and regulations. *Matrix Biol.* 2015;44:207-223. <https://doi.org/10.1016/j.matbio.2015.03.004>
53. Scheau C., Badarau I. A., Costache R. S., Caruntu C., Mihai G. L. [et al.] The role of matrix metalloproteinases in the epithelial-mesenchymal transition of hepatocellular carcinoma. *Anal. Cell. Pathol.* 2019;9423907. <https://doi.org/10.1155/2019/9423907>
54. Tsai H.-F., Trubelja A., Shen A. Q., Bao G. Tumour-on-a-chip: microfluidic models of tumour morphology, growth and microenvironment. *J. R. Soc. Interface.* 2017;14(131):20170137. <https://doi.org/10.1098/rsif.2017.0137>
55. Stoyanov E., Ludwig G., Mizrahi L., Olam D., Schnitzer-Perlman T. [et al.] Chronic liver inflammation modifies DNA methylation at the precancerous stage of murine hepatocarcinogenesis. *Oncotarget.* 2015;6(13):11047-11060. <https://doi.org/10.18632/oncotarget.3567>
56. Soria-Valles C., Gutiérrez-Fernández A., Osorio F. G., Carrero D., Ferrando A. A. [et al.] MMP-25 metalloproteinase regulates innate immune response through NF- κ B signaling. *J. Immunol.* 2016;197(1):296-302. <https://doi.org/10.4049/jimmunol.1600094>
57. Zhou J., Zheng X., Feng M., Mo Z., Shan Y. [et al.] Up-regulated MMP28 in hepatocellular carcinoma promotes metastasis via notch3 signaling and predicts unfavorable prognosis. *Int. J. Biol. Sci.* 2019;15(4):812-825. <https://doi.org/10.7150/ijbs.31335>
58. Fields G. B. The rebirth of matrix metalloproteinase inhibitors: moving beyond the dogma. *Cells.* 2019;8(9):984. <https://doi.org/10.3390/cells8090984>
59. Freitas-Rodríguez S., Folgueras A., Lopez-Otin C. The role of matrix metalloproteinases in aging: tissue remodeling and beyond. *Biochim. Biophys. Acta Mol. Cell. Res.* 2017;1864:2015-2025. <https://doi.org/10.1016/j.bbamcr.2017.05.007>

About authors:

Koroy Pavel Vladimirovich, MD, PhD, Professor of the Department of Hospital Therapy;
tel.: +78652713537; e-mail: paule75@yandex.ru; ORCID: 0000-0001-6392-8461

Dudov Temirlan Ruslanovich, Assistant of the Department of Hospital Therapy;
tel.: +78652713537; e-mail: timur222123@mail.ru

Yagoda Alexander Valentinovich, MD, PhD, Professor,
Honored Worker of Science of Russian Federation, Head of the Department of Hospital Therapy;
tel.: +78652295309; e-mail: alexander.yagoda@gmail.com; ORCID: 0000-0002-5727-1640

Sarithala Vijaya Jawahar, PhD, Assistant of the Department of Hospital Therapy;
tel.: +79887422198; e-mail: jay_sv2006@yahoo.com; ORCID: 0009-0001-9215-9021