MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN
CENTER OF MEDICAL EDUCATION
TASHKENT MEDICAL ACADEMY

METALLOPROTEINASE: structure, properties and role in the development of pathological conditions

Methodical recommendations

for graduate students and medical residents

Tashkent 2015

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Textbook is intended for master students, clinical residents of medical institutes. It shows the characteristics and properties of the matrix metalloproteinases, members of their family, inhibitors and their role in the development of pathological conditions, application of this topic in medicine, as well as control questions and tests on a given topic.

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Scientific secretary of the TMA, associate professor   Tashkenbaeva U.A

LIST OF ABBREVIATIONS

MMP - matrix metalloproteinases

IL - interleukins

TIMP - tissue inhibitors of MMPs

TNF - tumor necrosis factor

LPO - lipid peroxidation

cAMP - cyclic adenosine monophosphate

mRNA - The matrix ribonucleic acid

PAI-1 - plasminogen activator inhibitor type 1

BB - brain barrier

SOD - superoxide dismutase

ROS - reactive oxygen species

PG - perinatal hypoxia

CVD - cardiovascular disease

DHEA – dehydroepiandrosterone

Characterization of matrix metalloproteinases

Matrix metalloproteinases (MMP) - a group of zinc and calcium-dependent proteolytic enzymes that degrade various components of the extracellular matrix [Woessner JF, Jr. Matrix metalloproteinases and their inhibitors in connective tissue remodeling // FASEB J. 1991. T. 5. № 8. - C. 2145-54.]. MMP received its name for its ability to specifically hydrolyze the major proteins of the extracellular matrix [Nagase H. Matrix Metalloproteinases / H. Nagase, J.Woessner // J. Biol. Chem.-1999.-Vol. 274, N 31.-R. 21491-94.]. Matrix metalloproteases are a family consisting of 30 proteolytic enzymes in mammals predominantly detected. Most MMPs are synthesized as prepro and secreted as proenzymes. Activation of proMMP effected by plasmin or other MMP. Only a few of metalloproteinases known as membrane-type MMP secreted in a functionally active form [Solovyov NI Matrix metalloproteinases and their biological functions. Journal bioorgan Chemistry 1998; 24: 217-226.].

The structure of all MMP represented signal peptide necessary for secretion from cells successfully; propeptide portion (fig.), which when cleaved activates MMP; catalytic domain having coordination bonds with the cation zinc catalytic center, and a hinge region. The catalytic domain consists of two ion $Zn2+$ and $Ca2+$ ion is three. All enzymes except MMP-7 are like hemopeksin terminal domain containing a substrate binding site. In MMP-2, -9 identified secondary portion included in
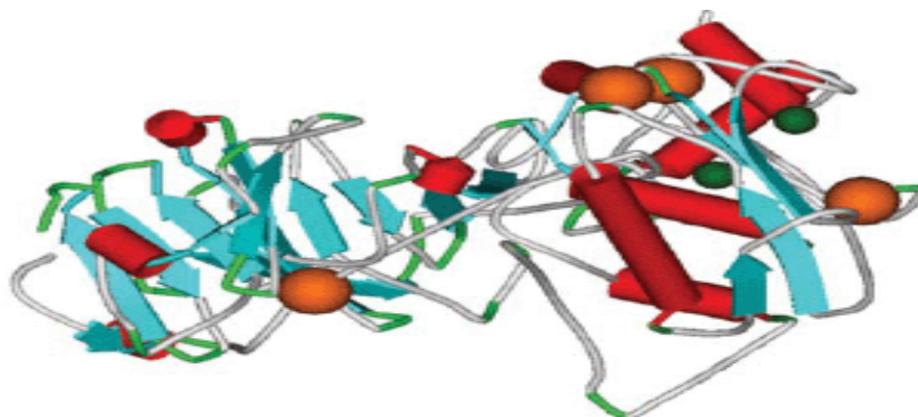
Three-dimensional structure of the proenzyme of MMP 1 person. Globule (PDB code 1su3) consists of two structural domains. N - terminal catalytic (right), and C terminal regulator (left). C - terminal domain determines the substrate specificity of the protease, as well as interact with TIMP proteins (MMP). Four Ca ion (large spheres) and two ion Zn (small dark spheres) essential for catalysis and stabilizing the globules MMPs.

catalytic domain similar to fibronectin type 2, which apparently provides a high affinity to membrane components gelatinases [Visse R. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemitry / R. Visse, H. Nagase // Circulation Res. - 2003. - N 2. - P.827-839.]. Propeptide contains a peptide sequence PRCGV / NPD, dubbed "cysteine switch" because it contains SH-group, which by binding to Zn2 + atom in the active center, support in the form of the molecule MMP zymogen (MMP precursor, inactive form). After hydrolytic removal of the propeptide and release of Zn2 + -binding center is activated MMP.

MMP involved in the remodeling and destruction of the extracellular matrix and cell membranes in different biological processes (skeleton formation, embryonic development, angiogenesis, ovulation, cell migration, breast development, wound healing, etc.) [Frankova J., Diamantova D., Vrbkova J., Ulrichova J. Influence of hydrogencalcium salts of oxidized cellulose on MMP-2, MMP-9 and TNF-alpha production and wound healing in non-healing wounds // Acta Dermatovenerol Croat. 2013. T. 21. № 4. - C. 219-23.]. In inflammatory processes metalloproteinases exhibit similar properties. They play an important role in the regulation of vascular permeability, breaking intercellular junctions between endothelial cells and promoting the migration of leukocytes into sites of inflammation. Metalloproteinases regulate the activity of inflammatory mediators - cytokines and chemokines [Manicone AM, McGuire JK Matrix metalloproteinases as modulators of inflammation // Semin Cell Dev Biol. 2008. V. 19. № 1. - C. 34-41.]. Recent studies have shown a direct and indirect effect on MMP-gated ion channels endothelial and vascular smooth muscle cells, as well as other mechanisms of expansion and contraction of blood vessels.

Metalloproteinases are composed of several groups, and their molecular structure, as a whole, characterized by 5 domains: this is the domain containing the signaling protein, required for secretion, a prodomain, a catalytic domain, hinge region and hemopexin-like domain. MMP-2 and MMP-9 differ from other MMP fibronektinopodobnyh having three modules (also known as type II modules fibronectin) involved in the binding of fibronectin to denatured collagen [Parks WC, Wilson CL, Lopez-Boado YS Matrix metalloproteinases as modulators of inflammation and innate immunity // Nat Rev Immunol. 2004. T. 4. № 8. - C. 617-29.].

All are relatively metalloprotease substrate specificity: collagenase subfamily representatives mainly responsible for the degradation of collagen I, II and III, gelatinases and stromelysins cleave collagen IV, V type, as well as elastin, fibronectin, laminin and gelatin. Substrates for MMP can also be nonmatric components: plasminogen, fibrin, fibronectin, casein, protein armature precursors cytokines. MMP-8, -12, -13, -14 inactivated coagulation factor XII, and MMP-1, -2, -3, -9, - interleukin IL-1β [Hiller O. Matrix metalloproteinases collagenase-2, macrophage elastase, collagenase- 3, and membrane type 1-matrix metalloproteinase impair clotting by degradation of fibrinogen and factor XII / O. Hiller [et al.] // J. Biol. Chem. - 2000. - Vol. 275. - P. 8-13.]. MMP-9 or gelatinase B, has a high affinity for the denatured collagen (gelatin), but is also able to cleave native collagen VI, V and XI types, elastin, and IL-8, connective tissue activating peptide III, Plate-factor-4, substance P-amyloid peptide β. Depending on where the splitting of these molecules MMP-9 may increase or decrease their biological activity [Van den Steen Ph. Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9) / Van den Steen Ph. [et al.] // Critical. Reviews in Biochem. and Molec. Biology. - 2002. - Vol. 37, N 6. - P. 375-536.].

The enzyme activity is dependent on the expression level of the genes and their availability activators and inhibitors. MMP referred to as "inducible" enzymes, transcription integer which obeys a number of factors (steroid and

thyroid hormones, cytokines, growth factors, and other chemical agents.). An exception is the MMP-2 expression of which occurs on constitutive way. These differences are explained in the regulation of transcription, in particular promoters of differences in the structure of the MMP. MMP expression similar to the expression of acute phase proteins and is regulated by inflammatory cytokines such as tumor necrosis factor α (TNF-α), TNF-γ and IL-1β [Frisch SM Transcription of the Stromelysin Promoter Is Induced by Interleukin-1 and Repressed by Dexamethasone / S. Frisch, H. Ruley // J. Biol. Chem. - 1987. - Vol. 262. - P.16300-304., MacNaul KL Discoordinate Expression of Stromelysin, Collagenase and Tissue Inhibitor of Metalloproteinases-1 in Rheumatoid Human Synovial Fibroblasts. Synergistic Effects of Interleukin-1 and Tumor Necrosis Factor-cx on Stromelysin Expression / K. MacNaul [et al.] // Biol. Chem. - 1990. - Vol. 265. - P. 17238-45.], Bacterial lipopolysaccharide [Cury JD Selective Up-Regulation of Human Alveolar Macrophage Collagenase Production by Lipopolysaccharide and Comparison to Collagenase Production by Fibroblasts / JD Cury [et al.] // Immunol. - 1988. - Vol. 141. - P. 4306-4312., Wahl L. Inhibition of phospholipase activity in human monocytes by IFN-y blocks endogenous prostaglandin E2-dependent colagenase production / L. Wahl [et al.] // Immunol. - 1990. - N 144. - P. 3518-22.]. Regulation of enzyme activity in the post-translational level by activation of zymogens or interaction with tissue inhibitors of MMPs (TIMMP) [Visse R. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemitry / R. Visse, H. Nagase // Circulation Res. - 2003. - N 2. - P.827-839.]. Precursors activated MMP extracellular environment primarily by plasmin or other proteases, including MMPs and tiolmodifitsiruyuschimi agents (4 aminofenilmerkurievy acetate, HgCl2 and N-etimaleimid). Low pH, hyperthermia and lipid peroxidation (LPO) can also activate metalloproteases [Solovyov NI Matrix metalloproteinases: regulation of activity and role in the process of carcinogenesis / NI Solovyov // Structure and function of proteolytic enzymes: Materials Conf. (11-13 October. 2000, Moscow). - M., 2000].

Members of the family of matrix metalloproteinases

Based substrat specify, nucleotide sequences, MMP divided into six groups: collagenases, gelatinases, stromelysins, matrilysin, membrane-associated and other metalloproteinases MMP [Lemaitre V., D'Armiento J. Matrix metalloproteinases in development and disease // Birth Defects Res C Embryo Today. 2006. T. 78. № 1. - C. 1-10.]. Table 1 presents a summary of the MMP.

The name of the enzyme	Abbreviation	The substrate on which the enzyme acts
collagenase		
collagenase visceral	MMP – 1	Collagen I, II, III, VII, X type, gelatin, MMP - 2 - 9
collagenase neutrophils	MMP – 8	Collagen I, II, III, V, VII, X type, gelatin
collagenase 3	MMP – 13	Collagen I, II, III, IV type gelatin, fibronectin, laminin
gelatinase		
gelatinase A	MMP – 2	Gelatin, collagen I, IV, V, VII, X, XI type, fibronectin, laminin, elastin
gelatinase B	MMP – 9	Gelatin, collagen, III, IV, V, VII, X types, elastin, vitronectin

stromelysin		
Stromelysin - 1	MMP – 3	Collagen III, IV, V, IX, X type, gelatin fibronetin, laminin, tenazin, MMP-1, -7, -8, -9, -13
Stromelysin – 2	MMP – 10	Collagen III, IV, V, IX-type gelatin, fibronetin, laminin, casein, MMP-1 -8
Stromelysin – 3	MMP – 11	Collagen IV, gelatin, fibronectin, laminin, α1-antiprotease and insulin-like growth faktorosvyazuyuschy protein-1
Membrane-associated metalloproteinases (MT-MMPs)		
MT – 1	MMP – 14	Collagen I, II, III type gelatin, fibronectin, laminin, vitronectin, proteoglycans activates pro-MMP-2 and pro-MMP-13
MT – 2	Activates pro-MMP-2	Activates pro-MMP-2
MT – 3	MMP – 16	Activates pro-MMP-2

MT – 4	MMP – 17	Activates pro-MMP-2
MT – 5 MT – 6	MMP – 24 MMP – 35	Activates pro-MMP-2 gelatinolytic activity
Do not belong to one of the groups		
	MMP – 12	Aggrecan, fibropektin, laminin and type IV collagenase
	MMP – 19	Gelatin tenaskin, laminin, aggrecan, type IV collagenase, nidogen
Enamilizin	MMP – 20	amelogenin
	MMP – 21	unknown
	MMP – 22	unknown
	MMP – 23A	unknown
	MMP – 23B	unknown
	MMP – 27	unknown
	MMP – 28	unknown

The precursor of matrix metalloproteinase-1 (proMMP-1) MMP-1 (also known as intestinal collagenase, collagenase spine fibroblast collagenase I) synthesized by fibroblasts, chondrocytes, macrophages, keratinocytes, endothelial cells and osteoblasts. MMP-1 synthesis is stimulated by different agents, including cytokines (e.g., epidermal growth factor, interleukins and TNF-α), and chemical compounds such as cAMP and phorbol esters. MMP-1 is inhibited by TIMP-1 and -2, and α2-macroglobulin. MMP-1 participates in the degradation of the collagen strands in the process of remodeling of the extracellular matrix.

MMP-1 levels determined in rheumatoid arthritis, osteoarthritis, tumor invasion, corneal ulceration, tissue remodeling, inflammatory bowel disease, atherosclerosis, aneurysm and restenosis. Moreover, MMP-1 can also cleave other substrates are casein, gelatin, entactin and cartilage link protein.

Matrix metalloproteinase-2 (MMP-2)

MMP-2 (gelatinase), primarily expressed in the mesenchymal cells (mainly fibroblasts) during tissue development and regeneration. Also synthesized by neutrophils, macrophages and monocytes. MMP-2 is required to inhibit angiogenesis in tumors, and its level is elevated in tumor vascular endothelium and in the urine of patients with different tumor entities.

Together with the MMP-9 is involved in the degradation of type IV collagen, a major component of basement membranes and gelatin (denatured collagen). MMP-2 may also disrupt other types of collagens (V, VII and X), elastin, and fibronectin. It is involved in the processing of many other molecules that modulate their function in different ways. For instance, it cleaves monocyte chemotactic protein-3, resulting in reduction of inflammation and provides vasoconstriction.

Matrix metalloproteinase-3 (MMP-3)

MMP-3, also known as stromelysin-1 catalyses the degradation of many components of connective tissue, including proteoglycan, link protein, collagen types II, IV, IX and XI, laminin and fibronectin.

MMP-3 may also affect the degradation of the extracellular matrix via activation prokollagenazy-1. MMP-3 is secreted as a 57 kDa proenzyme mass and in vivo activated by limited proteolysis of plasma and tissue endopeptidases. MMP-3 activity of TIMP inhibited which reacts with active MMP-3 in a stoichiometric ratio of 1: 1. It is believed that the balance between MMP-3 and TIMP - a determining factor in the destruction of the extracellular matrix. MMP-3 activity may also be inhibited by α2-macroglobulin. It is believed that MMP-3 plays an important role in the natural processes of tissue remodeling and pathological processes (rheumatoid arthritis and osteoarthritis).

Matrix metalloproteinase-7 (MMP-7)

MMP- 7 - one of the smallest MMPs, consisting of the pro-domain and a catalytic domain. MMP-7 is expressed in normal and pathological changes of epithelial cells. MMP-7 is synthesized by a variety of tumors: breast, colon, prostate, stomach, upper airway and esophagus, lung and skin. MMP-7 is able to utilize a large number of extracellular matrix proteins: collagen type IV, gelatin, laminin, aggrecan, entactin, elastin and verzikan. It activates other proteases: urokinase-type plasminogen activator and pro-MMP-1, -2, -9, and also destroys substrates type osteopontin. MMP-7-Fas-mediated destruction ligand protects tumor cells from chemotherapeutic drug and enhances apoptosis of epithelial cells.

Matrix metalloproteinase-8 (MMP-8)

MMP-8 (also known as neutrophil collagenase and collagenase 2) contained in the specific granules of polymorphonuclear leukocytes (PMNs) in an inactive zymogen. PMNs play an important role in phagocytosis and possess a high capacity for infiltration of the connective tissue. Various agents, such as IL-1 and IL-8, TNF-α, and GM-CSF stimulates the release of neutrophil MMP-8 - the key

enzyme budding of the extracellular matrix degradation, especially in pathological inflammatory conditions, rheumatoid arthritis and osteoarthritis. MMP-8 can cleave proteins such as fibronectin and cartilage aggrecan serpins, as well as the type of the angiotensin peptides, and substance P.

Matrix metalloproteinase-9 (MMP-9)

MMP-9 (also known as gelatinase B) is secreted as a zymogen mass of 92 kDa. Substrates for MMP-9 include denatured type I collagen (gelatin), native collagen types IV, V, VII, X and XI, fibrinogen, vitronectin, IL-1 and entactin which connects laminin and collagen type IV. MMP-9 is involved in the processes of inflammation, tissue remodeling and repair, mobilization matrix connected growth factors and cytokines processing. Her expression is correlated with desmoplasia (incorrect orientation of collagen) that accompanies cancer of the pancreas, lymph node metastases in breast cancer. The level of MMP-9 may increase in the fluid of the teeth-gums and saliva of patients with gingivitis and periodontal disease.

Matrix metalloproteinase-10 (MMP-10)

MMP-10 (also known as stromelysin-2 and tranzin-2) is expressed by osteoclasts, cells, tumors of the head, neck, and human lung. Excess of MMP-10 expression in the corneal epithelium of patients with diabetes may be a major cause of observed changes in diabetic retinopathy.

Active MMP-10 is capable of cleaving several proteins involved in wound healing: collagen type III and type IV, gelatin, nidogen, laminin-1, elastin and proteoglycans. Active enzyme also activates pro-MMP-1, -7, -8 and -9.

Matrix metalloproteinase-13 (MMP-13)

MMP-13, also known as collagenase 3, has a broad substrate specificity, and play an important role in invasion and metastasis of tumors. The purified enzyme is a monomeric MM 19.6 kDa. Initially, MMP-13 has been found in breast tumors. Further studies showed that the enzyme is produced by a large number of different

malignant cells, including squamous head and neck tumors, where increased expression of MMP-13 represents an increased invasiveness of the tumor, squamous cell carcinoma of the upper respiratory tract, vulva and larynx. Recent studies have shown that MMP-13 is diagnostically important marker for prostate cancer and targets for monitoring patients after xenotransplantation in breast cancer. Increased expression is associated with aggressive tumor with carcinoma of the esophagus. MMP-13, together with the other MMPs, is involved in extracellular matrix degradation gum periodontitis.

MMP-13 activity is associated with a poor prognosis in colorectal cancer survival. Endothelial cells of the skin are also a source of MMP-13. Enhanced expression of the enzyme under conditions conducive to the growth of vascular endothelial cells and differentiation. Communication overexpression of MMP-13 with non-healing wounds is shown by the example of chronic skin ulcers. A growing number of studies that confirm the important role of MMP-13 in the development of rheumatoid arthritis and osteoarthritis.

MMP activity under physiological conditions is regulated by a number of specific inhibitors, primarily tissue inhibitor of metalloproteinase (TIMP). It is now well studied TIMP-1, TIMP-2, TIMP-3 and TIMP-4, which differ from the specific effect on the metalloproteinase (Table. 2). Thus, TIMP-1 inhibits most active MMP-9, while TIMP-2 inhibits the activity of MMP-2 [Bobkov IN, Kozlovsky, LV, Lee O. The role of matrix metalloproteinases in the pathogenesis of renal disease. Ter architect in 2008; 6: 86-90.].

Table 2

Substrate specificity of TIMP-1, -2, -3, -4 [Shestakov MV Santa II Diabetes and chronic kidney disease. M: MIA 2009., Anderson SS, Wu K., Nagase H. et al.

Eff ect of matrix glycation on expression of type IV collagen, MMP-2, MMP-9 and TIMP-1 by human mesangial sells. Cell Adhes Commun 1996; 4: 2: 89-101].

Inhibitor	Substrat
TIMP-1	Forms a non-covalent complex with all active MMPs, except MT1-, MT3-, MT5-MMP. The highest affinity - MMP-1, -2, -8, -13, -18, stromelysin-1.
TIMP -2	Complexed with MMP-9 activity by blocking its activation stromelysins Active against all of MMP with high specificity to inhibit MMP-2
TIMP -3	Preferably inhibits MMP-1, -2, -3, -9. It has high affinity to matrix components, exhibits inhibitory activity of binding sites with them
TIMP -4	Inhibits MMP different, the most - MMP-2

All TIMPs are composed of two domains, six fixed by disulfide bonds. One domain is mainly responsible for inhibition, whereas the other domain can bind to the pro-gelatinases, as well as stimulate cell proliferation. All connective tissues contain TIMPs. Main place of expression of TIMP-1 are found in the ovaries and bone. TIMPs inhibit tumor growth, metastasis and angiogenesis. TIMP-1 promotes MMP-1 synthesis in fibroblasts.

Tissue inhibitor of metalloproteinase-2 (TIMP-2)

The expression of TIMP-2 is observed in normal and tumor tissues. The concentration of TIMP-2 in serum correlates with the duration of both remission and survival in patients with breast cancer.

Serum TIMP-2 levels are elevated in patients with systemic sclerosis. Intend to use this test to measure the degree of malignancy of the tumor.

Tissue inhibitor of metalloproteinase 4 (TIMP-4)

TIMP-4 mRNA was expressed at high levels in the heart at low levels in kidney, pancreas, testes, and colon. The level of TIMP-4 in plasma is decreased in patients with hypertrophic obstructive cardiomyopathy after ethanol ablation of the interventricular septum, indicating the important role of TIMP-4 in myocardial remodeling. Furthermore, the expression of TIMP-4 is broken at the different types of tumors, including breast cancer, cervical and endometrial cancer, glioma, and choriocarcinoma.

An important inhibitor of MMPs is plasminogen activator inhibitor type 1 (PAI-1) capable of blocking plasminogen activators urokinase and tissue types, and prevent the formation of plasmin. Blocking like plazmin , PAI-1 inhibits the activation of MMPs. Another mechanism of inhibitory effect associated with the ability to connect to the urokinase-type plasminogen activator. This prevents the activation of urokinase-induced MT1-MMP, which is formed by a functionally active form of MMP-2 [Bobkov IN, Kozlovsky, LV, Lee O. The role of matrix metalloproteinases in the pathogenesis of renal disease. Ter architect in 2008; 6: 86-90.]. MMP activity can also inhibit α2-macroglobulin, megzinom and other inhibitors [Bobkov IN, Kozlovsky, LV, Lee O. The role of matrix metalloproteinases in the pathogenesis of renal disease. Ter architect in 2008; 6: 86-90., Ohtomo S., Nangaku M., Izuhara Y. et al. The role of megsin, a serine protease inhibitor, in diabetic mesangial matrix accumulation. Kidney Int 2008; 74: 6, 768-774.].

In recent years, experimental studies aimed at understanding of the mechanism of hypoxic damage to the blood-brain barrier (BBB), we study the matrix metalloproteinases (MMPs) - a family of enzymes that degrade extracellular matrix proteins [Greenlee KJ, Werb Z., Kheradmand F. Matrix metalloproteinases in lung: multiple , multifarious, and multifaceted // Physiol. Rev. 2007. V. 87. P.

69-98.]. Established that MMPs play an important role in several physiological and pathological processes, including embryogenesis, wound healing, inflammation, cardiovascular disease, pulmonary disease and cancer [Chakraborti S., Mandal M., Das S. et al. Regulation of matrix metalloproteinases: an overview // Mol. Cell Biochem. 2003. V. 253. P. 269-285.]. One of the enzymes of this family - MMP-9 degrades collagen type IV, which is the main component of cerebral endothelial basement membrane, and thus creates conditions for the migration of cells across the BBB [Lukes A., Mun-Bryce S., Lukes M. et al. Extracellular matrix degradation by metalloproteinases and central nervous system diseases // Mol. Neurobiol. 1999. V. 19. P. 267-284.].

MMP activity is regulated by tissue inhibitors of metalloproteinases [Cunningham LA, Wetzel M., Rosenberg GA Multiple roles for MMPs and TIMPs in cerebral ischemia // Glia. 2005. V.50. P. 329-339.]. Another no less important regulators of the activity and synthesis of MMP, according to experimental studies are reactive oxygen species (ROS) [Nelson KK, Melendez JA Mitochondrial redox control of matrix metalloproteinases // Free Radic. Biol. Med. 2004. V.37. № 6. P. 768-784.], The effects of which are limited to non-enzymatic antioxidants and enzyme [Dröge W. Free radicals in the physiological control of cell function // Physiol. Rev. 2002. V. 82. P. 47-95.]. It can be assumed that the enzyme superoxide dismutase (SOD), which inactivates superoxide radical can prevent activation and induction of the synthesis of matrix metalloproteinases.

In a state of hypoxia in the body of preterm infants develop oxidative stress due to increased production of ROS and antioxidant system immaturity [Dennery PA Role of redox in fetal development and neonatal diseases // Antioxid. Redox Signal. 2004. V. 6. P. 147-153.]. It was found that in the development of hypoxic-ischemic encephalopathy and intraventricular hemorrhage with PG plays an important role due to the AFC free-radical oxidation of biomolecules [Ferriero DM Neonatal brain injury // N. Engl. J. Med.2004. V. 351. P. 1985-1995.]. Furthermore, in recent years shows that ROS are regulators of the activity of

several enzymes, including MMPs and by specific oxidation of thiol groups of proteins can alter the conformation of protein transcription factors that lead to their activation or Inga-birovaniyu [Dröge W. Free radicals in the physiological control of cell function // Physiol. Rev. 2002. V. 82. P. 47-95.]. Thus, direct activating effect on AFC MMP was observed upon incubation of purified extracellular matrix metalloproteinase precursor pro-MMP-2 and pro-MMP-9 from human smooth muscle system xanthine - xanthine [Rajagopalan S., Meng XP, Ramasamy S. et al. Reactive oxygen species produced by macrophagederived foam cells regulate the activity of vascular matrix metalloproteinases in vitro: implications for atherosclerotic plaque stability // J. Clin. Invest. 1996. V. 98. P. 2572-2579.]. It is shown that hydrogen peroxide and other ROS induce translocation into the nucleus of the activator protein-1, a nuclear transcription factor κB (NF-κB) transcription factor and ERK ½ with a consequent increase in MMP activity. On the other hand, it was reported that MMP-9 was induced and post ischemic cerebral edema damage to the BBB [Gasche Y., Fujimura M., Morita-Fujimura Y. et al. Early appearance of activated matrix metalloproteinase-9 after focal cerebral ischemia in mice: a possible role in blood-brain barrier dysfunction // J. Cereb. Blood Flow Metab. 1999. V.19. P. 1020-1028., Romanic AM, White RF, Arleth AJ et al. Matrix metalloproteinase expression increases after cerebral focal ischemia in rats: inhibition of matrix metalloproteinase-9 reduces infarct size // Stroke. 1998. V. 29. P. 1020-1030., Svedin P., Hagberg H., Savman K. et al. Matrix metalloproteinase-9 gene knock-out protects the immature brain after cerebral hypoxia-ischemia // J. Neurosci. 2007. V. 27. P. 1511-1518.], And the increased concentration of MMP-9 in plasma is a predictor of neurological disorders in neonates with asphyxia [Sunagawa S., Ichiyama T., Honda R. et al. Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 inperinatal asphyxia // Brain & Development. 2009. V. 31.P. 588-593.]. Conversely, inhibition of MMP-9 gene knockout and MMP-9 in the experiment was reduced post-ischemic brain damage [Romanic AM, White RF, Arleth AJ et al. Matrix metalloproteinase expression increases after cerebral focal ischemia in rats: inhibition of matrix metalloproteinase-9 reduces

infarct size // Stroke. 1998. V. 29. P. 1020-1030., Svedin P., Hagberg H., Savman K. et al. Matrix metalloproteinase-9 gene knock-out protects the immature brain after cerebral hypoxia-ischemia // J. Neurosci. 2007. V. 27. P. 1511-1518.].

Given these facts, as well as data about the suppression of the activation of MMP-9 non-enzymatic antioxidant N-acetylcysteine in the in vitro [Galis ZS, Khatri JJ Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly // Circ. Res. 2002. V. 90. P. 251-262.], It has been suggested that the antioxidant enzymes, including SOD, which acts as the first line of defense against ROS tissues [Fridovich I. Superoxide anion radical (O2 • -), superoxide dismutases, and related matters // J. Biol. Chem. 1997.V. 272, № 30. P. 18515-18517.], Can limit the ability of developing GHG with inadequate synthesis of MMP activation and thereby prevent them from damaging effect on the BBB with perinatal hypoxia. To test the hypothesis that the interaction of the antioxidant system with a system of MMPs in the pathogenesis of perinatal hypoxia (GHG) emissions were measured concentrations of MMP-9 and TBRP simultaneously with the activity of SOD in the blood plasma of two groups of preterm infants with PG and without clinical signs of GHGs.

And secretion of MMP activity in normal tissue - very low [Nagase H., Woessner JF, Jr. Matrix metalloproteinases // J Biol Chem. 1999. T.274. № 31. - C. 21491-4.]. Basic regulation occurs at the level of transcription of mRNA [Toth PP Subclinical atherosclerosis: what it is, what it means and what we can do about it // Int J Clin Pract. 2008. V. 62. № 8. - C. 1246-54.]. Gene expression of metalloproteinases regulate various growth factors (epidermal GF, basic fibroblast GF, plateled-derived GF), cytokines (TNF-α, IL-1β), as well as chemical agents or physical stress. Extracellular stimuli through signaling pathways leading to activation of the transcription factor AP-1 binding sites which have only MMP-1,3,7,8,9,10,11,12 and MMP-13. Expression of AP-1 induced MAP kinases through extracellular signalregulationkinase (ERK 1 and 2), stress-activated protein kinase (SAPK) and p38 [Chambers M., Kirkpatrick G., Evans M., Gorski

G., Foster S., Borghaei RC IL-4 inhibition of IL-1 induced Matrix metalloproteinase-3 (MMP-3) expression in human fibroblasts involves decreased AP-1 activation via negative crosstalk involving of Jun N-terminal kinase (JNK) // Exp Cell Res. 2013. T. 319. № 10. - C. 1398-408 .; Tseng HC, Lee IT, Lin CC, Chi PL, Cheng SE, Shih RH, Hsiao LD, Yang CM IL-1beta promotes corneal epithelial cell migration by increasing MMP-9 expression through NF-kappaB- and AP-1-dependent pathways // PLoS One. T. 2013. 8. № 3. - C. e57955.].

After synthesis of MMP zymogen form found in intercellular spaces. At that time, when an additional signal to arise through activation of reactive oxygen species, ischemia triggers (protease thrombin or chymotrypsin) or angeotenzin-converting enzyme from mast cells, opens the active site of the enzyme [Stewart JA, Jr., Wei CC, Brower GL, Rynders PE, Hankes GH, Dillon AR, Lucchesi PA, Janicki JS, Dell'Italia LJ Cardiac mast cell- and chymase-mediated matrix metalloproteinase activity and left ventricular remodeling in mitral regurgitation in the dog // J Mol Cell Cardiol. 2003. T. 35. № 3. - C. 311-9.].

Metalloproteinases have an important role in many normal physiological processes such as embryonic development, morphogenesis, reproduction, and tissue remodeling, as well as in various pathological processes: arthritis, malignant growth, and cardiovascular diseases. The amount of newly synthesized MMPs regulated mainly at the transcriptional level, and the proteolytic activity of MMPs existing controlled as proenzymes activation and inhibition of active enzymes endogenous inhibitor, α2-macroglobulin and tissue inhibitors of metalloproteinases (TIMPs). Specificity MMPs can be divided into collagenase (MMP-1, -8 and -13), gelatinases (MMP-2 and -9) and stromelysins (MMP-3 and -10).

Collagenase cleaved collagen types 1-3, 7 and 10, gelatinase - type 4 collagen and denatured collagens. Stromelysins destroy fibronectin, laminin, collagen, 4, 5 and 7, type, and proteoglycans (see. Table.). In addition to the similarity at the amino acid sequence, all MMPs are produced from inactive precursors which are converted into active protease under the influence of

extracellular factors. MMRs are many sources of cells, including fibroblasts, macrophages, smooth muscle cells of the vascular wall, the neutrophils; their production is increased under the influence of cytokines. Given that MMRs actively synthesized under the action of inflammatory cytokine level determination their precursors can be used to evaluate the activity of these regulators.

MMPs and cardiovascular disease

The study Atherogene found that MMP-9 and TIMP-1 are independent predictors of cardiovascular disease (CVD) and cardiovascular death in patients with coronary artery disease. In the normal vascular wall can be found only MMP-2, TIMP-1 and -2, whereas most other MMRs are defined only in atheroma. The level of MMP-9 is higher, the greater the volume of atherosclerotic coronary lesions. Shown a significant increase in the level of MMP-9 and TIMP-1 in atherosclerosis compared with patients with effort angina and healthy people. This gives reason to use these two proteins as markers of the acute phase (plaque rupture). Elevated levels of MMP-9 has a prognostic value in relation to the development of restenosis. Several studies have shown significant increase of MMP-2 in myocardial infarction patients compared with healthy individuals.

MMRs and Oncology

Showed that the expression of MMP-2 and -9 plays an important role in the metastasis of lung and squamous carcinoma of the cervix, breast tumors, bladder cancer, RCC, and the expression of MMP-1 - tumor metastasis in lung and breast .

MMRs and bone disease

MMRs form a large area of bone resorption complexes consisting of two molecules of a C-telopeptide of type I collagen, the other segment helical collagen molecules and cross-linking between the pyridine. These complexes are designated CTX-MMP, enter the bloodstream and then excreted in urine. However, their structure is unstable, and they are destroyed by the action of cathepsin K and

proteolytic enzymes in the bloodstream, resulting in blood circulate different C-telopeptide fragments. When osteoarthritis is shown elevated levels in tissues and synovial fluid of many MMRs and activators of pro-MMRs, including general activator MMRs plasmin. The relative scarcity of TIMP promotes increased proteolysis in the cartilage in osteoarthritis. Previously it was thought that the main role in the degradation of the matrix belongs to MMP-1, was then established the important role of MMP-13, which breaks down collagen type II, and MMP-3.

MMRs and reproduction

MMRs activate tissue changes during the menstrual cycle, have the ability to break down the extracellular matrix, including the basement membrane. After involution of the corpus luteum or cancellation of exogenous steroids endometrium rejected. This process is stimulated endometrial MMRs that rise after discontinuation of progesterone. MMRs destroying extracellular matrix and contribute to the rejection of the upper two-thirds of the endometrium. In endometrial stromal cells detected MMP-1-3, -9 and -11. There's also synthesized TIMP, but their production is not regulated by steroid hormones. Cyclic MMRs development plays an important role in the invasion of heterotopic endometrial and development of endometriosis. For genital endometriosis MMRs appear in high concentrations and promote proliferation heterotopias progression in the abdominal cavity. MMP-2 content in the peritoneal fluid and plasma is significantly higher in women with endometriosis than in the control group. Many studies have shown that the pathological processes in the womb are directly related to the change in the content of the uterus MMP-2 and -9. Their level is significantly higher in the pathology.

MMRs and sepsis

Currently in sepsis great importance is attached chemoattractant (substances responsible for the infiltration of neutrophils, and mobilization of the affected lung tissue). These include, in particular, neutrophil chemoattractant tsitokinin (CINC) and a group of MMRs (MMP-9, MMP-2). These mediators produced in response

to entering the body LPS; no accident, pulmonary neutrophilic infiltration is characteristic of acute lung injury with gram-negative sepsis.

The role of metalloproteinases in the pathogenesis of psoriasis and atherosclerosis

MMP participate in a wide range of biological processes associated mainly with the degradation of extracellular matrix components, presupposes the existence of a balance between MMP and their natural inhibitors (TIMP). Imbalance between them gives rise to a pathology, in particular, to the development of different vascular diseases such as aortic aneurysm, varicose veins, atherosclerosis and hypertension [Raffetto JD, Khalil RA Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease // Biochem Pharmacol. 2008. V. 75. №2. - C. 346-59.]. For example, in atherosclerosis was shown that MMP actively participate in different stages of its development. MMP activation leads to changes in the structure of atherosclerotic plaques, and can lead to rupture. Disruption of atherosclerotic plaques occurs when exposed to proteases its fibrous cap facing the lumen of the vessel, which may lead to the development of acute myocardial infarction and sudden cardiac death [Takahashi H., Tsuji H., Hashimoto Y., Ishida-Yamamoto A., Iizuka H . Serum cytokines and growth factor levels in Japanese patients with psoriasis // Clin Exp Dermatol. 2010. T. 35. № 6. - C. 645-9.]. The extracellular matrix is produced by smooth muscle cells are mainly synthetic type located in the intima of arteries, include collagen I, III, IV, V, VIII type, and laminin. Collagen type I and III are synthesized and localized in the intima and fibrous plaques, while the edge portions plaques contain large amounts of collagen, procollagen type I cells sintes [Adiguzel E., Hou G., Sabatini PJ, Bendeck MP Type VIII collagen signals via beta1 integrin and RhoA to regulate MMP-2 expression and smooth muscle cell migration // Matrix Biol. 2013. T. 32. № 6. - C. 332-41 .; Mannello F., Medda V., Ligi D., Raffetto J.D. Glycosaminoglycan sulodexide inhibition of MMP-9 gelatinase secretion and activity: possible pharmacological role against collagen degradation in vascular

chronic diseases // Curr Vasc Pharmacol. 2013. T. 11. № 3. - C. 354-65 .; Yang M., Du GP, Wang LQ, Wang XP, Cui FZ, Lu YJ, Huang YF [The expression level of MMP-2 and collagen of hydroxyapatite modified titanium for keratoprosthesis in the corneal stroma of rabbits] // Zhonghua Yan Ke Za Zhi. 2013. T. 49. № 10. - C. 914-20.].

Metalloproteinase involved in the remodeling after myocardial infarction, which can lead to dilated cardiomyopathy. Ventricular remodeling after myocardial infarction, or viral damage also occurs under the influence of MMP, which destroy frame of elastin and collagen, leading to ventricular dilation and hypertrophy. As the severity and range of cardiovascular disease varies from acute conditions such as myocardial infarction, sudden cardiac death, chronic diseases (atherosclerosis), myocardial remodeling and inflammation come out on top. Tissue remodeling - two-stage process: cellular component changes in the structure and the change in the structure of the matrix. The extracellular matrix is now seen as a direct participant in organ function and changes in its structure, and matrix metalloproteinases - as mediators of its remodeling.

Recent studies indicate the role of MMP in the process and on the potential use in diagnostic and therapeutic purposes. Currently, matrix metalloproteinase identified as potential biomarkers of cardiac complications in the destruction of atherosclerotic plaques. Metalloproteinase considered as a point of action for correcting changes in atherosclerotic lesions of the coronary vessels. Thus, by increasing the expression of MMP-12 and monocytic infiltration occurs vascular wall, leading to rupture of the inner wall of the elastic layer and accelerate the atherosclerotic process [Liang J., Liu E., Yu Y., Kitajima S., Koike T., Jin Y., Morimoto M., Hatakeyama K., Asada Y., Watanabe T., Sasaguri Y., Watanabe S., Fan J. Macrophage metalloelastase accelerates the progression of atherosclerosis in transgenic rabbits // Circulation. 2006. T. 113. № 16. - C. 1993-2001 .; Motterle A., Xiao Q., Kiechl S., Pender SL, Morris GE, Willeit J., Caulfield MJ, Ye S. Influence of matrix metalloproteinase-12 on fibrinogen level // Atherosclerosis.

2012. T. 220. № 2. - C. 351-4.]. In turn, the structural integrity of the plaque is also dependent on the balance between the processes of synthesis and destruction of the extracellular matrix, which is mainly regulated through interaction with their MMP inhibitors (TIMP). Thus, it was shown that the plaques whose integrity has been violated in a complex MMP-9 / TIMP- 1 expression level maintains the balance towards increasing the expression of MMP-9, compared to the plaques which were not destroyed. At the same time there was decrease in TFPI-2 (Tissue factor pathway ingibitor) [Higashikata T., Yamagishi M., Higashi T., Nagata I., Iihara K., Miyamoto S., Ishibashi-Ueda H., Nagaya N., Iwase T., Tomoike H., Sakamoto A. Altered expression balance of matrix metalloproteinases and their inhibitors in human carotid plaque disruption: results of quantitative tissue analysis using real-time RT-PCR method // Atherosclerosis. 2006. T. 185. № 1. - C. 165-72.]. Thus, the extremely high expression of MMP leads to the destruction of the extracellular matrix of blood, causing the separation of plaque, leading in most cases to myocardial infarction [Kunz J. Matrix metalloproteinases and atherogenesis in dependence of age // Gerontology. 2007. V. 53. № 2. - C. 63-73.].

The level of expression of MMP-1,3,9 mRNA and TIMP-1 in significantly material carotid plaques, whereas the expression level of TFPI-2 has been reduced. Partial MMP-9 expression and imbalance MMP9 / TIMP-1 may play a pivotal role in the destruction of the plaque.

In the development of many diseases have been identified elevated levels of expression of some MMP. The most studied in this respect were cancer, cardiovascular diseases and arthritis. In different types of cancer were MMP-1, 2, 3, 7, 9, 10, 11, 13 and 14 [Kerkela E., Saarialho-Kere U. Matrix metalloproteinases in tumor progression: focus on basal and squamous cell skin cancer // Exp Dermatol. 2003. T. 12. № 2. - C. 109-25.]. MMP can promote tumor growth not only by the degradation of the extracellular matrix, but with the release of isolated growth factors [108]. Thus, MMP-9 of VEGF mobilizes extracellular matrix and decomposes type IV collagen, forming an angiogenic inhibitor - tamstatin

[Higashikata T., Yamagishi M., Higashi T., Nagata I., Iihara K., Miyamoto S., Ishibashi-Ueda H ., Nagaya N., Iwase T., Tomoike H., Sakamoto A. Altered expression balance of matrix metalloproteinases and their inhibitors in human carotid plaque disruption: results of quantitative tissue analysis using real-time RT-PCR method // Atherosclerosis. 2006. T. 185. № 1. - C. 165-72.].

In biology, skin MMP involved in the remodeling of the inflamed matrix, the formation of new blood vessels, healing of wounds and malignant transformation [Suomela S., Kariniemi AL, Snellman E., Saarialho-Kere U. Metalloelastase (MMP-12) and 92-kDa gelatinase (MMP- 9) as well as their inhibitors, TIMP-1 and -3, are expressed in psoriatic lesions // Exp Dermatol. 2001. T. 10. № 3. - C. 175-83.]. Psoriasis is histologically characterized by hyperproliferation of keratinocytes, infiltration by inflammatory cells, neoangiogenesis skin vascular dilation and production of cytokines such as TNF-a, IL-1b, TGF-a and INF-g in the same transcriptional regulation of MMP. Many of these factors as well take part in the healing of skin wounds by precise regulation of MMP [Blaha K., Borsky J., Kasparova M., Steklacova A., Zajickova V., Pechova M., Matejova R., Kotaska K., Dostalova T. Concentrations of MMP-9 and TIMP-1 in lip tissue and their impact on cleft lip surgery healing // Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013. T. 157. № 4. - C. 363-6 .; Davis ME, Gumucio JP, Sugg KB, Bedi A., Mendias CL MMP inhibition as a potential method to augment the healing of skeletal muscle and tendon extracellular matrix // J Appl Physiol (1985). 2013. T. 115. № 6. - C. 884-91.]. Many cytokines or growth factors, which are marked hyperproduction psoriasis (TNF-a, IL-1, INF-g, IL-6, IL-8, VEGF, TGF-a) can also regulate the production MMP.

Stromelysin-1 (MMP-3) and 2 (MMP-10), matrilysin (MMP-7) metalloelastase (MMP-12) are often grouped according to their subgroup stromelysin and substrate-structure. MMP-3 and MMP-10 may be expressed by epithelial cells. MMP-3 fibronectin and tenascin destroys levels which increased in

the skin of patients with psoriasis [Buommino E., De Filippis A., Gaudiello F., Balato A., Balato N., Tufano MA, Ayala F. Modification of osteopontin and MMP- 9 levels in patients with psoriasis on anti-TNF-alpha therapy // Arch Dermatol Res. 2012. T. 304. № 6. - C. 481-5.].

Element of the subgroup stromelysins - MMP-12, the most active MMP against elastin [Shapiro SD Matrix metalloproteinase degradation of extracellular matrix: biological consequences // Curr Opin Cell Biol. 1998. T. 10. № 5. - C. 602-8 .; Yang M., Du GP, Wang LQ, Wang XP, Cui FZ, Lu YJ, Huang YF [The expression level of MMP-2 and collagen of hydroxyapatite modified titanium for keratoprosthesis in the corneal stroma of rabbits] // Zhonghua Yan Ke Za Zhi. 2013. T. 49. № 10. - C. 914-20.]. It can also disrupt the structure of fibronectin, collagen type 4, laminin-1, as well as activate TNF-α [Chandler S., Cossins J., Lury J., Wells G. Macrophage metalloelastase degrades matrix and myelin proteins and processes a tumour necrosis factor-alpha fusion protein // Biochem Biophys Res Commun. 1996. T. 228. № 2. - C. 421-9 .; Gronski TJ, Jr., Martin RL, Kobayashi DK, Walsh BC, Holman MC, Huber M., Van Wart HE, Shapiro SD Hydrolysis of a broad spectrum of extracellular matrix proteins by human macrophage elastase // J Biol Chem. 1997. T. 272. №18. - C. 12189-94.]. Previous studies have shown that macrophages - the main source of MMP-12.

Neutrophils and macrophages are one of the key cells involved in the formation of psoriatic infiltrate.

Activated neutrophils are able to influence not only on the growth and differentiation of keratinocytes, but also to activate T-cells [Terui T., Ozawa M., Tagami H. Role of neutrophils in induction of acute inflammation in T-cell-mediated immune dermatosis, psoriasis: a neutrophil-associated inflammation-boosting loop // Exp Dermatol. T. 2000. 9. № 1. - C. 1-10.].

Expression of matrix metalloproteinases is mainly regulated at the transcriptional level, so the levels of MMP correlate well with the level of RNA matrix [Morimoto Y., Oyabu T., Ogami A., Myojo T., Kuroda E., Hirohashi M.,

Shimada M., Lenggoro W ., Okuyama K., Tanaka I. Investigation of gene expression of MMP-2 and TIMP-2 mRNA in rat lung in inhaled nickel oxide and titanium dioxide nanoparticles // Ind Health. 2011. T. 49. № 3. - C. 344-52 .; Taniguchi S., Ryu J., Seki M., Sumino T., Tokuhashi Y., Esumi M. Long-term oral administration of glucosamine or chondroitin sulfate reduces destruction of cartilage and up-regulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Hartley guinea pigs // J Orthop Res. 2012. T. 30. № 5. - C. 673-8.]. According to one study mRNAMMP-3 was odnaruzhena in 19% of samples of the skin manifestations of atherosclerosis [Suomela S., Kariniemi AL, Snellman E., Saarialho-Kere U. Metalloelastase (MMP-12) and 92-kDa gelatinase (MMP-9) as well as their inhibitors, TIMP-1 and -3, are expressed in psoriatic lesions // Exp Dermatol. 2001. T. 10. № 3. -C. 175-83.] AmRNAMMP 12 - 77% of cases. A significant increase in the level of expression of this metalloprotiinazy observed in all sites of inflammation. This study demonstrated that MMP-12 positive cells in this case are macrophages. It was noted that MMP-3 and MMP-12 is not expressed by normal skin [Chen CL, Liou SF, Chen SJ, Shih MF Protective effects of Chlorella-derived peptide on UVB-induced production of MMP-1 and degradation of procollagen genes in human skin fibroblasts // Regul Toxicol Pharmacol. 2011. T. 60. № 1. -C. 112-9 .; Huang J., Luo X., Lu J., Chen J., Zuo C., Xiang Y., Yang S., Tan L., Kang J., Bi Z. IPL irradiation rejuvenates skin collagen via the bidirectional regulation of MMP -1 and TGF-beta1 mediated by MAPKs in fibroblasts // Lasers Med Sci. 2011. T. 26. № 3. - C. 381-7.].

Expression of TIMP-1 marked inflammatory infiltrates in endothelial cells and in 75% of cases. The most precise data were obtained in patients who are taking corticosteroids topically. Changes in the level of expression of TIMP-3 noted in 50% of samples, while also observed changes in expression levels in samples of healthy skin, blood vessels and a perivascular stroma hair follicles [Airola K., Ahonen M., Johansson N., Heikkila P., Kere J. , Kahari VM, Saarialho-Kere UK Human TIMP-3 is expressed during fetal development, hair growth cycle, and cancer progression // J Histochem Cytochem. 1998. T. 46. №4. - C. 437-

47.]. TIMP-1 is expressed in normal skin fibroblasts separate [Frost J., Ramsay M., Mia R., Moosa L., Musenge E., Tikly M. Differential gene expression of MMP-1, TIMP-1 and HGF in clinically involved and uninvolved skin in South Africans with SSc // Rheumatology (Oxford). 2012. T. 51. № 6.-C. 1049-52.].

It is shown that MMP-12 and MMP-9 are expressed most intensely in the centers of psoriatic skin lesions. MMP-1,7,10,13 less associated with the disease [Suomela S., Kariniemi AL, Snellman E., Saarialho-Kere U. Metalloelastase (MMP-12) and 92-kDa gelatinase (MMP-9) as well as their inhibitors, TIMP-1 and -3, are expressed in psoriatic lesions // Exp Dermatol. 2001. T. 10. № 3. -C. 175-83.].

Due to its ability to degradation of elastin fibers MMP-12 promotes macrophage migration to other tissue. Activated macrophages are the first cells that fall into the epidermis of psoriatic plaques when a [Frost J., Ramsay M., Mia R., Moosa L., Musenge E., Tikly M. Differential gene expression of MMP-1, TIMP-1 and HGF in clinically involved and uninvolved skin in South Africans with SSc // Rheumatology (Oxford). 2012. T. 51. № 6. -C. 1049-52.]. In the study of cell cultures contacted with T-cells macrophages increase the expression of MMP-12. There overexpression IL-1b, VEGF granulocyte / macrophage colony stimulating factor (GM-CSF) in psoriasis, which increases expression of MMP-12 by macrophages [Cherng JY, Chen LY, Shih MF Preventive effects of beta-thujaplicin against UVB-induced MMP-1 and MMP-3 mRNA expressions in skin fibroblasts // Am J Chin Med. 2012. T. 40. № 2. - C. 387-98 .; Frost J., Ramsay M., Mia R., Moosa L., Musenge E., Tikly M. Differential gene expression of MMP-1, TIMP-1 and HGF in clinically involved and uninvolved skin in South Africans with SSc // Rheumatology (Oxford). 2012. T. 51. № 6. -C. 1049-52 .; Oriana S., Guendalina L., Oscar C., Antonio Z., Fiorenza O., Mauro P., Roberto DP, Andrea G., Annamaria O. Delayed wound healing in aged skin rat models after thermal injury is associated with an increased MMP-9, K6 and CD44 expression // Burns. 2013. T. 39. № 4. - C. 776-87.].

To activate MMP-12 is required urokinase-type plasminogen activator [Carmeliet P., Moons L., Lijnen R., Baes M., Lemaitre V., Tipping P., Drew A., Eeckhout Y., Shapiro S., Lupu F. , Collen D. Urokinase-generated plasmin activates matrix metalloproteinases during aneurysm formation // Nat Genet. 1997. T. 17. № 4. - C. 439-44.], And its level is increased in psoriasis. In addition, MMP-12 may increase the inflammatory response by stimulating the production of TNF-alfa proTNF of-a [Chandler S., Cossins J., Lury J., Wells G. Macrophage metalloelastase degrades matrix and myelin proteins and processes a tumour necrosis factor -alpha fusion protein // Biochem Biophys Res Commun. 1996. T. 228. № 2. - C. 421-9.]. It is noted that, to increase the expression of MMP-12 alone is insufficient kerotinotsits hyperproliferation.

When keratinocyte hyperproliferation decreased level of expression of MMP-9, compared with normal keratinocytes.

MMP-12 has an anti-angiogenic effect due to cleavage of plasminogen to angiostatin [Cornelius LA, Nehring LC, Harding E., Bolanowski M., Welgus HG, Kobayashi DK, Pierce RA, Shapiro SD Matrix metalloproteinases generate angiostatin: effects on neovascularization // J Immunol. 1998. T. 161. № 12.-C. 6845-52.]. Increased expression of TIMP-1 and MMP-12 may not be specific.

Increased activity of MMP is a key element in the development of the pathogenesis of HIV-associating gingivitis, periodontitis and HIV by the associated dementia. - 1990. - N 144. - P. 3518-22.].

Successful implantation of the embryo in vitro fertilization (IVF) depends on the respective state of the uterus and its receptor sensitivity. A successful process of implantation of the embryo depends on the activity of MMPs, cytokines, prostaglandins, molecules "adhesion". In the group of patients who were not able to get pregnant despite a 10-fold procedure of IVF program, there has been a significant increase in the concentration of MMP-2, -9, IL-1 and TNF several times as compared with the control group of women who did not have a history of violations of the process of embryo implantation [Inagaki N. Analysis of intra-

uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer / N. Inagaki [et al.] // Human Reproduction. - 2003. - Vol. 18, N 3. - P. 608-615.]. Collagen I, III and V types responsible for the structural integrity and strength of endometrial tissue, collagen type IV improves trophoblast invasion. MMP-2 triggers the degradation of the extracellular matrix in the ovaries, providing normal ovulation. In biopsies of uterine epithelium transcript levels of collagen type 1 and MMP-2 is higher in women with a diagnosis of idiopathic infertility (despite normal folliculogenesis, the menstrual cycle and the absence of adhesions) and especially increased in women with multiple recurrent miscarriages. Increased activity and MMP-2, TIMP reduction prevents the normal process of blastocyst invasion [Jokimaa V. Altered expression of genes involved in the production and degradation of endometrial extracellular matrix in patients with unexplained infertility and recurrent miscarriages / V. Jokimaa [et al.] // Molec. Human Reproduction. - 2002. - Vol. 8, N 12. - P.1111-16.].

Expression, content and activity of MMPs are regulated by sex hormones [Natoli AK Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloproteinase expression / A. Natoli [et al.] // Hypertension. -2005. - N 46. - P. 1129-34.]. The presence of estrogen and progesterone in cultured endometrial cells reduces the activity of metalloproteases, but the abolition of hormone activity increases sharply, which in turn is accompanied by morphological changes in the cells of the endometrium, uterine epithelium characteristic for the period of menstruation [Marbaix E. The expression of interstitial collagenase in human endometrium is controlled by progesterone and by estradiol and is related to menstruation / E. Marbaix [et al.] // Biochem. J. - 1995. - Vol. 305. - P. 1027-30., Irwin JC Human endometrial matrix metalloproteinase-2, a putative menstrual proteinase. Hormonal regulation in cultured stromal cells and messenger RNA expression during the menstrual cycle / JC Irwin [et al.] // J. Clin. Invest. - 1996. - Vol. 97, N 2. - P. 438-447.]. Using the rabbit endometrium as research material showed that the greatest progesterone reduces MMP expression, and also increases the transcription of genes encoding

TIMP [Takashi Sato. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 / Takashi Sato [et al.] // Biochem. J. - 1991. - Vol. 275. - P. 645-650.]. The high correlation between increased serum prolactin levels and increased activity of TIMP-1 in the ovaries of rats [Hirsch B. Stimulation of matrix-metalloproteinase-1 and tissue inhibitor of metalloproteinase-1 gene expression in rats by the preovulatory prolactin peak / B. Hirsch [et al.] // European Journal of Endocrinology. - 1999. - Vol. 140. - P. 583-589.]. In the cell culture in the presence of prostate cancer metiltrinolona, mibolerona (drugs with high androgen index), and in particular of dehydroepiandrosterone (DHEA) showed a reduction in MMP-1, -3 and -7, which inhibits tumor progression [Schneikert J. Androgen Receptor-Ets Protein Interaction Is a Novel Mechanism for Steroid Hormone-mediated Down-modulation of Matrix Metalloproteinase Expression / J.Schneikert [et al.] // J. Biolog. Chemistry. - 1996. - Vol. 271, N 39. - R. 1203-9.]. In the experiment, the rats receiving DHEA had 4-fold lower levels of MMP-2 mRNA and a 2-fold lower levels of active forms of MMP-2 than in the control group.

Tireodnyh influence of hormones on the activity of MMPs detected in an experimental model of primary hypothyroidism in rats. Using propiluratsila (inhibits peripheral conversion process of T4 to T3) recorded a five-fold increase in the activity of MMP-2, MMP-3, -14, reduction of collagen 1, 3 types and reducing the level of TIMP-1 in ovarian tissue in rats [Samir Kumar Saha. Differential Expression of Procollagen Lysine 2-Oxoglutarate 5-Deoxygenase and Matrix Metalloproteinase Isoforms in Hypothyroid Rat Ovary and Disintegration of Extracellular Matrix / Samir Kumar Saha [et al.] // Endocrinology. - 2005.- Vol. 146, N 7. - P. 2963-75.]. Reduction of T3 leads to increased degradation of the extracellular matrix of rat ovarian MMP, which disrupts the normal architecture of tissues and functions, and thus folliculogenesis.

Thus, these data suggest indisputable involvement of the IMF in the development of many pathological processes. Determination of the activity, the

content of mRNA for MMPs expression is useful to determine the stage of transformation of chronic hepatitis to cirrhosis of the liver, diabetic complications: nephropathy, diabetic retinopathy and destabilization of atherosclerotic plaque, tumor growth, and many others.

Determination of the activity of metalloproteinases

Metalloproteinase activity when examined by ELISA kit for quantifying human / murine pro and active matrix metalloproteinase-2 (MMP-2 total) in human serum, plasma, saliva, urine, cell culture supernatants and murine sera (ZAO "BioKhimMak").

PRINCIPLE OF THE METHOD. This test is based on the method of quantitative ELISA "sandwich". The microplate was covered with specific polyclonal antibodies to MMP-2. During the reaction wells in standards and samples added, and MMP-2 present in the sample binds to the immobilized antibody. After washing, all unbound components are removed, and the conjugate added to the wells of polyclonal antibodies to MMP-2 enzyme. After the second wash and remove unbound antibody-enzyme conjugate is added to a substrate solution that reacts with the enzyme to form a colored complex. The intensity of color is directly proportional to the concentration of total MMP-2 (pro- and active MMP-2) connected to the first stage. The color reaction was stopped stop reagent and the color intensity is measured on a tablet photometer.

Control questions:

1. What enzymes are matrix metalloproteases?

2. Jonah any metals includes the catalytic domain of metalloproteinase?

3. What are the processes involved MMP?

4. How many domains molecule consists of metalloproteinases?

5. Do the substrate specificity of metalloproteinase?

6. Based substrat specify, nucleotide sequences into groups divided as metalloproteinase?

7. Do the substrate specificity of TIMP?

8. Is the MMP inhibitor plasminogen activator inhibitor type 1?

9. If any pathologies any changes Activity of MMP?

10. The principle of the method of quantitative ELISA metalloproteinases?

Examples of situational problems:

1. Which family of enzymes are involved in the destruction of the organic components of connective tissue?

A: Matrix Metalloproteinases, they belong to the family of $Zn2+$ -and $Ca2+$ - dependent endopeptidases involved in connective tissue remodeling by breaking its organic components at physiological pH values. MMP received its name for its ability to specifically hydrolyze the major proteins of the extracellular matrix

2. What determines the enzyme activity of metalloproteinase?

A: The enzyme activity is dependent on the expression level of the genes and their availability activators and inhibitors. Regulation of enzyme activity in the post-translational level by interaction with tissue inhibitors of MMPs. Degradation of the extracellular matrix, MMP adjustment is needed for the occurrence of many physiological processes.

3. What is the role of metalloproteases in joint destruction in arthritis?

Answer: a metalloprotease involved in joint destruction in arthritis. A significant increase of MMP activity in the blood plasma of patients with rheumatoid arthritis. Revealed overexpression of mRNA for MMP-1, -3 in the inflamed synovium. Level of enzyme activity in cartilage correlates with the severity of joint damage. Low activity of MMPs in serum creates the danger of excessive formation of proliferative processes with the development of resistant strains and fibrotic contracture of the affected joints.

4. What is the role of metalloproteases in the development of diabetic nephropathy?

Answer: High concentrations of glucose reduces the secretion of MMPs and inhibit their proteolytic activity in diabetes. Decrease in enzyme activity leads to a

proliferation of mesangial cells, the accumulation of proteins MM, basement membrane thickening and obliteration of the glomerular capillaries. These disorders affect the filtration capacity and hemodynamics glomeruli in patients with diabetic nephropathy.

5. What is the role of metalloproteases in the development of malignant tumors?

A: metalloprotease involved in the processes of carcinogenesis by acting on different signal transduction pathways in cells, the major components of MM on cell-cell interactions as well as producing different biologically active molecules. In patients with bronchoalveolar carcinoma revealed a significant level of expression of MMP-2, -9 tumor cells, resulting in high invasiveness and motility of tumor.

6. What is the role of the metalloproteases in the development of atherosclerosis?

Answer: The high activity of MMPs is observed in atherosclerotic hearth. Macrophages of atherosclerotic plaques produce a significant amount of MMP. Protease initiate the process of destroying the structure of atheroma, increase its mobility, the probability of separation from the vessel wall and the appearance of emboli that can cause clogging of blood vessels. Assignment of low doses of doxycycline for 6 months reduces MMP-2, -9 atheroma in vessels, and, hence, the gap preventiruet plaque.

7. What is the role of metalloproteases in the development of stomach cancer?

Answer: The high activity of MMP-9 was found in gastric cancer and is in strict correlation with the degree of tumor progression, angiogenesis and concomitant malignancy. Furthermore MMP-9 tumor cells expressing gastric MMP-2, which is not determined in normal tissue. Moreover, the mRNA levels of MMP-2 forms with low-grade cancer is much lower than the poorly differentiated forms, as well as metastasis.

8. What is the role of metalloproteases in the development of HIV-associating gingivitis?

Answer: Increased MMP activity is a key element in the development of the pathogenesis of HIV-associating gingivitis, periodontitis and HIV by the associated dementia. In the latter case, the virus causes a change in the activity of MMP-2, -9, -14 in brain tissue with consequent damage to the extracellular matrix, blood-brain barrier, the migration of macrophages and proliferation of glia.

9. What is the role of metalloproteases in vitro fertilization?

Answer: The successful implantation of the embryo in vitro fertilization (IVF) depends on the respective state of the uterus and its receptor sensitivity. A successful process of implantation of the embryo depends on the activity of MMPs,

cytokines, prostaglandins, molecules "adhesion". Collagen I, III and V types responsible for the structural integrity and strength of endometrial tissue, collagen type IV improves trophoblast invasion. MMP-2 triggers the degradation of the extracellular matrix in the ovaries, providing normal ovulation.

Test questions:

1. Give the correct definition of matrix metalloproteinases (MMP)?

- A group of zinc and calcium-dependent proteolytic enzymes that degrade various components of the extracellular matrix.

- A group of zinc and calcium-dependent proteolytic enzymes that degrade various components of the intracellular matrix.

- A group of zinc and iron-dependent coenzymes that degrade various components of the cell membrane.

- A preprotein that are synthesized using metal ions.

2. How is the activation of proMMP?

- Under the action of plasmin or other MMP.

- Inhibition of proteolytic enzymes by

- Using MMP proteins.

- Activation of MMPs is regulated by the central nervous system.

3. Functions of the MMP:

- Involved in the remodeling and degradation of the extracellular matrix and in cell membranes of various biological processes

- Participate in the formation of ketone bodies.

- Activate inflammatory mediators as vasopressin and chemokine

- Affect the ion channels of the intestines

4. Select the correct molecular structure of the IMF?

- Characterized 5th domains: this is the domain containing the signaling protein, the prodomain, a catalytic domain, hinge region and hemopexin-like domain.

- Characterized by a 6-domains: domain ligand connector a part predomen, catalytic domain, hinge region and hemopeksino-like domain.

- It consists of 3 main domains: a catalytic domain and the chemokine prodomain.

- Has a quaternary molecular structure similar to hemoglobin.

5. Specify the properties that characterizes all metalloprotease?

- Have relative substrate specificities.

- Proenzymes.

- Have absolute substrate specificity.

- Have a similar structure with proteolytic fermentama.

6. substrates for MMPs could be:

- Plasminogen, fibrin, fibronectin.

- Casein, fibronectin gemoglabin.

- Core protein precursors of cytokines and immunoglobulins.

- Sodium, calcium and iron.

7. On the basis of what MMP divided into six groups?

- Based on the nucleotide sequences and substrat specify.

- On the basis of catalytic function and nucleotide sequences.

- Based on the molecular structure and function.

- Based substrat specify and specificity.

8. Name the substrate which acts on the enzyme MMP - 1:

- Collagen I, II, III, VII, X type, gelatin, MMP - 2 - 9.

- Collagen I, II, III, V, VII, X types of gelatin.

- Collagen I, II, III, IV type, gelatin, fibronectin, laminin.

- Gelatine, collagen I, IV, V, VII, X, XI type, fibronectin, laminin, elastin.

9. stromelysin - 1 influences:

- Tenazin, MMP-1, -7, -8, -9, -13.

- Laminin, casein, MMP-1, -8.

- A1-antiprotease and insulin-like growth factor connector protein-1.

- Activates pro- MMP-2 and pro-MMP-13.

9. What types of matrix metalloproteinases that are not related to any of the groups:

- MMP - 12, MMP - 19, MMP - 20, MMP - 21, MMP - 22.

- MMP - 1, MMP - 8, MMP - 13, MMP - 2.

- MMP - 9, MMP - 3, MMP - 10, MMP - 11.

- MMP - 14, MMP - 15, MMP - 16, MMP - 17, MMP - 18.

10. The synthesis of MMP-1 is stimulated by various agents such as:

- Epidermal growth factor, interleukins and TNF-α.

- And fibroblast collagenase I.

- Insulin-like growth factor connector protein -1.

- Stromelysin - 1.

11. The level of MMP-1 was determined by:

- Rheumatoid arthritis and osteoarthritis.

- At various hepatitis

- In oncology

- In immunodeficiency.

12. MMP-2 is synthesized:

- Neutrophils, macrophages and monocytes.

- Nephrocytes, macrophages and epithelial cells

- Red blood cells, macrophages and monocytes

- Neutrophils, and microphages makrolitami.

13. The main function of MMP-3 (stromelysin-1)?

- Catalyzed degradation of connective tissue components.

- Participates at inflammatory processes.

- Increases the activity of ketone bodies.

- Controls the growth of bone.

14. The matrix metalloproteinase-8 (MMP-8) it?

- Neutrophil collagenase and collagenase 2.

- One of the smallest MMP.

- Stromelysin-1.

- Gelatinase B.

15. Specify the properties of the tissue inhibitor of metalloproteinase - 1 (TIMP)?

- Forms a non-covalent complex with all active MMPs.

- Inhibits mainly MMP-1, -2, -3, -9.

- Inhibits MMP different, the most - MMP-2.

- It has a high affinity to matrix components, exhibits inhibitory activity to their binding sites.

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