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Matrix metalloproteinase 9: A Representative Diagnostic Biomarker for Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Annotation
Matrix metalloproteinase 9 is a proteolytic enzyme which is recently one of the more often studied biomarkers. Its possible use as a biomarker of neuronal damage in stroke, heart diseases, tumors, multiple sclerosis, and epilepsy is being widely indicated. In epilepsy, MMP-9 is suggested to play a role in epileptic focus formation and in the stimulation of seizures. The increase of MMP- 9 activity in the epileptic focus was observed both in animal models and in clinical studies. MMP-9 contributes to formation of epileptic focus, for example, by remodeling of synapses. Its proteolytic action on the elements of blood-brain barrier and activation of chemotactic processes facilitates accumulation of inflammatory cells and induces seizures. Also, modification of glutamatergic transmission by MMP-9 is associated with seizures.

Key words: Matrix metalloproteinase-9, neuroinflammation, epilepsy, hippocampal sclerosis

Introduction

Discovered in 1974 matrix metalloproteinase 9 (MMP-9), also known as gelatinase B, belongs to the superfamily of proteolytic enzymes, degrading extracellular matrix and influencing almost all aspects of mammalian cell biology.

The characteristic structure of this group of enzymes is based on a prodomain and a catalytic domain containing zinc, to which other domains distinguishing different families and enzymes are attached. Belonging to the family of gelatinases MMP- 9 is one of the most complex matrix metalloproteinases. In its structure, apart from the prodomain and the catalytic domain, a fibronectin-like, a hemopexin, and a type V collagen-like domain are included [1]. The presence of MMP-9 was shown within the hippocampus, cerebral cortex, and cerebellum [3]. The expression of MMP-9 was observed in neural and glial cells [4]: above all in astrocytes and microglia [5]. Within the cell the presence of the active form of MMP-9 was confirmed in nucleus of neurons and glia [6, 7]. In the synapses the presence of MMP-9 mRNA, protein, and enzymatic activity was shown in dendritic spines containing the postsynaptic part of excitatory synapses [4, 8–10]. Moreover, inflowing leukocytes are the source of MMP-9 in CNS [11]. MMP-9 is also secreted by endothelial cells [12]. Small amount of protease is released constantly, though its level and activity rise significantly after various stimuli, both physiological and pathological [13].

The secretion of MMP-9 is regulated on many levels. Gene expression for MMP-9 within the brain is dependent mainly on two transcription factors: activator protein 1 (AP-1) and nuclear factor-κB (NF-κB).An increase of MMP-9 expression in neurons is induced by their depolarization and activation of receptors [14, 15]. In microglial cells, inflamma- tory factors cause the increase of MM СЧР-9 expression. Transcription is influenced by various cytokines, chemokines and growth factors. In human neural cells interleukin- (IL-) 1β increases transcription of MMP-9 and transforming growth factor β (TGF-β) inhibits it [11]. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) increase expression and activity of MMP-9 [9].

MMP-9 is secreted from neurons (dendrites) under the influence of glutamate [21]. MMP-9 is released in an inactive form. The activation of MMP-9 is reached in two ways. The first is cleaving of the propeptide. This role may be fulfilled by different metalloproteinases—mainly MMP-3—and com- ponents of plasminogen-plasmin cascades. The other way of activation is lysis of cysteine residue [12]. The activity of MMP-9 is

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inhibited by endogenous proteins TIMPs. Among them TIMP-1 is considered to be a natural inhibitor of MMP-9. The misbalance between MMP-9 and TIMP is associated with numerous CNS diseases [23]. MMP-9 exerts its effects mostly in the extracellular space [3]. However, possibility of its actions inside the cells was also described (e.g., [24]; for molecular biology of MMP-9, see [15]).

According to recent studies, MMP-9 seems to be a key factor in pathogenesis of epilepsy. It is assumed that impaired plasticity within the synapse and mossy fibers sprouting within the hippocampus, both associated with MMP-9 activity, have an impact on the formation of a new epileptic focus [6–8]. The other kind of process interrelated with epileptogenesis is inflammatory processes within CNS, whose regulation is also influenced by MMP- 9 activity. Additionally, MMP-9 is associated with blood- brain barrier damage which lowers seizure threshold and induces formation of new epileptic foci [10]. In next paragraphs the effects of MMP-9 activity and its associations with epilepsy will be presented.

Role of matrix metalloprotease Extracellular Matrix. One of the activities of MMP-9 is lysis of the extracellular matrix (ECM). Noteworthy, ECM is not only a passive scaffolding on which other functional elements are deployed. The main components of ECM are proteoglycans, hyaluronic acid, link proteins, and tenascins. Proteoglycans mainly belong to the family of hyalectans binding with hyaluronic acid in macromolecular complexes with help of link proteins [11]. So far its inhibitory effect on axon growth in in vitro research has been reported (e.g., [12]). Proteoglycans also exert a plasticity-limiting effect in CNS and change the ECM composition to characteristic for adults [13]. Tenascins are macromolecular glycoproteins able to bind with adhesion molecules and surface receptors [13]. Apart from these main elements, ECM comprises, for example, laminin, thrombospondin, lectins, and matrix metalloproteinases.

The components of ECM participate in regulation of ion homeostasis, which is being suggested for example, on the basis of initial axonal segment formation on the foundation of ECM proteins. Recently also the questions of probable neuroprotective activity of perineuronal nets (PNN) are being taken into concern. The PNN are big aggregates of ECM, surrounding subpopulations of neurons, which according to recent data exert neuroprotective effect in neurotoxicity caused by amyloid-β. Their neuroprotective activity against oxidative stress has also been suggested [5]. ECM is also said to be the forth part of the synapse (apart from the pre- and postsynaptic part of neurons and a glial cell) which modulates activity of ion channels and receptors within the synapse [6]. Among the components of ECM influencing synaptic changes and in consequence formation of new epileptic foci, MMP-9 attracts much attention .

Changes within the synapse associated with epilepsy are exerted in dendritic spines . Modification of their morphology is linked with MMP-9 activity . Michaluk et al. noted that in neural cells of the hippocampus chronic enzymatic activity of MMP-9 causes elongation and thinning of dendritic spines. Temporary increase of the MMP-9 level on the other hand induces their growth and change of shape to a mushroom-like. The presence of MMP-9 is essential for dendritic spines growth. The change of dendritic spines' morphology is caused by MMP-9 activity and is mediated by β-dystroglycan, intercellular adhesion molecule 5 (ICAM-5), and β1, β2, and β4 integrins [42– 48]. After cleaving of neuroligin 1 by MMP-9 modification of synaptic transmission was observed. The modification was associated with a change in the presynaptic part . Another substrate of MMP-9 responsible for changes in synapse structure and activity is synaptic cell adhesion molecule-2 (synCAM-2) [50]. Additionally, MMP-9 cleaves a postsynaptically localized protein, nectin-3 [1], and proteins responsible mainly for intrasynaptic transmission: β-amyloid peptide [2], insulin-like growth factor-binding proteins [3], and IL-1β [4]. Also the change of the structure of dendritic spines may influence transmission within the synapse.

MMP-9 affects induction of long-term potentiation (LTP), a main model of synaptic plasticity, changing simultaneously structure and functioning of the synapse . As is noted by Matsuzaki et al. [5] the induction of LTP is associated with enlargement and remodeling of small dendritic spines presenting only N-methyl-D-aspartate (NMDA) receptors to big synapses presenting both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The activity of NMDA receptors in turn modifies the levels and activity of MMP-9 what may be a significant step in generating LTP [6]. After the seizures the activity of MMP-9 associated with AMPA and NMDA receptors increases [9]. MMP-9 causes degradation of amyloid precursor protein what influences the secretion of soluble amyloid precursor protein α, associated with neuronal plasticity and memorization, and LTP within the hippocampus [7]. Noteworthy, MMP-9 affects

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both LTP induction and its maintenance [8]. In MMP-9 knockout mice a dysfunction of the late phase of LTP was noted , similarly as it was reported in animals in which MMP-9 was inhibited by TIMP-1 or a MMP-9 specific inhibitor . The influence of MMP-9 on LTP is still being analyzed; however, it has to be noted that, by regulation of LTP, MMP-9 modifies processes of learning and memory.

Research carried out so far indicate that MMP-9 plays a vital role in spatial and appetitive memory. The inhibition of MMP-9 leads to LTP abnormalities within the hippocampus and in consequence influences memorizing of localization in space. The appetitive memory is associated with the expectation of reward and development of addiction. The activity of MMP-9 is increased within the central nucleus of the amygdala and is essential to memorizing associated with the expectation of reward [61].

Other Functions. MMP-9 takes part in many physiological processes: cell differentiation and migration, tissue healing and remodeling, cytokine secretion, regulation of growth factors activity, and regulation between pro- and anti-inflammatory processes and between the processes of survival and apoptosis. So far the role of MMP-9 has been reported, for example, in oligodendrocyte differentiation, Schwann cell migration , neuronal regrowth, degradation of active NGF, or conversion of pro- BDNF [4]. In MMP-9 knockout mice a delay of migration and a decrease of apoptosis of cerebellar granule cells were reported. Some of the aforementioned effects, that is, Schwann cell migration and neuronal regrowth, are the effects of nonenzymatic activity of MMP-9.

MMP-9 participates also in many pathological processes. Among others its role was noted in cancerogenesis and metastasis, pathology of learning and memory, addiction, and psychiatric diseases (schizophrenia, bipolar disorder, and cognitive disorders) as well as in inflammatory and neurodegenerative diseases, multiple sclerosis, and cerebral ischemia [2].

Epileptic Focus. In the context of epilepsy the effect of MMP-9 was noted in tissue remodeling within the epileptic focus after the occurrence of seizures. In the study of Szklarczyk et al. [1] an association between remodeling within dentate gyri and an increased expression and activity of MMP-9 was reported after the kainate-induced seizures in rats. A greater susceptibility to epileptogenic process was observed in transgenic rats which exhibited overexpression of the active form of MMP-9 in the kindling model induced by pentylenetetrazole [8]. Also other researchers noted the association of MMP-9 with reorganization of neuronal cir- cuits [4]. Impaired synaptic plasticity is essentially linked with epilepsy. During kindling, which is a repeated brain stimulation, it comes to lowering of the seizure threshold and eventually to spontaneous occurrence of epileptic seizures. On the cellular level mossy fiber sprouting and formation of new synaptic connections are then being observed [3].

Inflammation. The other effect associated with epilepsy is the activation of inflammation. Numerous studies uncover an increase of the level or activity of MMP-9 aft r the induction by inflammatory factors. MMP-9 affects inflammatory processes on many levels; for example, it enables leukocyte influx to the locus of inflammation through the blood-brain barrier, helps to form the chemotactic signal by releasing the chemokines from ECM, and activates tumor necrosis factor α (TNF-α). Recently its double role in the regulation of pro- and anti-inflammatory processes has been noted. An example of that role is not only intensification, but also inhibition of chemotaxis by MMP-9 [7]. Lo et al. note that the activity of MMP-9 in acute inflammation may be an attempt of rescuing the healthy tissues. Additionally, it was observed that factors that are said to be proinflammatory not always intensify the epileptic process; active microglia may also exert protective function during status epilepticus. It seems that MMP-9 may be partially responsible for the maintenance of homeostasis between protection and damage.

When it comes to the prevalence of inflammatory processes a new epileptic focus is being formed. In the inflamed tissue microglia is being activated and astrocytes become reactive. The presence of reactive astrocytes was observed in epileptic foci in temporal epilepsy, focal cortical dysplasia, or tuberous sclerosis. These cells produce proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) responsible for the promotion of cell death after status epilepticus. Moreover they secrete chemokines, recruiting inflammatory cells, for example, C-C motif chemokine ligands 2, 3, and 5 [83] what leads to further intensification of inflammatory processes. MMP-9 takes part in activation and deactivation of many chemokines and cytokines participating in inflammation, for example, IL-1β, TNF-α, and TGF-β [12, 14, 15].

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MMP-9 plays a vital role in blood-brain barrier damage. The increase of blood-brain barrier permeability is one of the first abnormalities which occur in status epilepticus. On the other hand, malfunctioning of blood-brain barrier causes lowering of seizure threshold independently of the cause of disruption , contributes to induction of epileptic discharges, and increases their frequency [6]. MMP-9 is a main factor participating in blood-brain barrier damage independently of the damaging factor [7]. The role of MMP- 9 in blood-brain barrier disruption was reported in cerebral ischemia and inflammation.

MMP-9 causes damage to blood-brain barrier by cleaving zonula occludens 1 protein, one of the proteins regulating efficiency of tight junctions. Moreover, collagen type IV, a main component of the basal lamina of endothelium, is a substrate for MMP-9 [11]. Opposing results concern occludin, a building block of tight junction connections, which is another protein on which the tightness of blood-brain barrier is dependent. In the research of Asahi et al. MMP- 9 influence on the occludin level was not confirmed, what on the contrary was observed by Reijerkerk et al. and Zozulya et al.

Released from the leukocytes during inflammation MMP-9 may be a factor promoting the inflammatory process by influencing blood-brain barrier permeability and enabling further influx of the cells participating in inflammation [12]. The role of tissue invading leukocytes in epileptic process comes to attention of, for example, Fabene et al.. The enzymatic activity of metalloproteinases is vital for leukocyte migration .

MMP-9 takes part both in chemotaxis and in migration of inflammatory cells. MMP-9 activates, for example, IL-8, granulocyte chemotactic protein, and many others. In a mouse model of meningitis crossing the endothelium by leukocytes contributes to further damaging of blood-brain barrier and induction of epileptic seizures [9]. Leukocytes biphasically influence formation of epileptic focus. In the acute phase they exacerbate the damage of blood-brain barrier. In the chronic phase they contribute to the release of cytokines, chemokines, and cytotoxic enzymes. They also cause changes in vessels and influence production of free oxy- gen radicals. The permeability of blood-brain barrier has influence on dendritic cell migration as well. Produced by dendritic cells MMP-9 mediates their migration .

Glutamatergic Receptors. The effect of MMP-9 on glutamate receptors may also impact neuronal excitability and development of seizures. MMP-9 modifies both NMDA and AMPA receptors influencing the efficiency of glutamatergic transmission . MMP-9 increases the activity of NMDA receptor through integrins. After inhibition of integrin $\beta 1$ with simultaneous presence of MMP-9 a total immobilization of NMDA receptor was observed. The EphB receptor and β-dystroglycan, molecules affecting the activation of NMDA receptor, are substrates for MMP-9. Also MMP-9 itself influences NMDA receptor causing its activation [59]. On the other hand, activation of NMDA receptor has influence on the expression and activity of MMP-9 [15] as well as on the modification of adhesion molecules and change of the morphology of dendritic spines. MMP-9 cleaves an adhesion molecule ICAM-5 whose soluble extracellular domain affects the expression of AMPA receptor within the synapse. Acting through the integrins MMP-9 decreases the activity of AMPA receptor. As it has been shown so far, MMP-9 modifies glutamatergic transmission and influences the quantity of glutamate within the synapse.

Cell Death. It is being suggested that, in some models of epilepsy, MMP-9 contributes to cell death. In a kainate- induced seizure model MMP-9 causes cell death in the mechanism of excitotoxicity. In a model of status epilepticus induced by pilocarpine, Kim et al. reported cell death in a mechanism of apoptosis associated with MMP- 9 activity. Apart from epilepsy models MMP-9 was observed to cause cell death contributing, for example, to impairment of transmission between ECM and the cell through the lipoprotein receptor-related protein, separation of the cells from ECM leading to anoikis, the kind of apoptosis caused by the activation of proteolytic cascades an increase of calpain activation, and initiation of caspase cascade and induction of cytotoxicity.

The main source of information about the cerebral structure morphology in patients with epilepsy is specimens excised during neurosurgical operations. The patients qualified for the operation most frequently are diagnosed with drug- resistant epilepsy which is defined as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”. Other patients qualified for the neurosurgical procedures are diagnosed

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with complex epileptic syndromes, for example, Lennox-Gastaut syndrome, or suffering from other diseases in which epileptic seizures such as tuberous sclerosis or Sturge-Weber syndrome occur [12].

Approximately 73% of patients qualified for neurosurgical operation are diagnosed with temporal lobe epilepsy (TLE) . TLE is frequently associated with selective atrophy of the hippocampus, the hippocampal sclerosis. The histopatho- logical picture of TLE with coexisting hippocampal sclerosis comprises neuronal loss, abnormalities of morphology and function of various receptors and channels, activated neuro- genesis and formation of new synaptic connections, gliosis, inflammatory processes, and blood-brain barrier damage [12]. However, independently of hippocampal sclerosis loss of neurons and changes of synapse organization is reported also in other epileptic foci. Additionally there appear neurons of changed morphology; for example, in the amygdala they are smaller and have less first-row dendritic spines while the total number of dendritic spines is increased.

The most frequent form of focal epilepsy is mesial temporal lobe epilepsy (MTLE). In patients with MTLE with coexisting hippocampal sclerosis the MMP-9 activity was reported to be increased within neural and glial cells within CA1 and CA2 regions off hippocampus, in the granule cell layer of dentate gyrus and in the neocortex . Additionally, the researchers observed a correlation between the localization of TIMP-1 and the activity of MMP-9 in neocortex. The results of the study seem to be in favor of the association of MMP-9 with drug-resistant MTLE and coexisting hippocampal sclerosis. In another study in patients with MTLE associated with hippocampal sclerosis a decreased level of the collapsin response mediated protein-2 (CRMP-2) was reported [8]. CRMP-2 is a crucial protein for axonal regrowth and maintenance of neuronal polarity within the hippocampus. CRMP-2 is also a substrate for MMP-9. An increased activity of MMP-9 may be a cause of neuronal plasticity disorders and their degeneration may be mediated by the degradation of CRMP-2.

In TLE an increased expression of the proinflammatory cytokines IL-1β and NF-κB was reported. On the other hand the increased expression of these cytokines causes an increase of MMP-9 level. A similar rise in the proinflammatory cytokine level was also found in focal cortical dysplasia and tuberous sclerosis , disorders associated with occurrence of seizures. The level of MMP-9 activity was increased within the epileptic foci of patients with focal cortical dysplasia and tuberous sclerosis as well. Interestingly, an increase of MMP-9 activity was also reported in the unchanged tissue of patients with epilepsy [10]. In the study of Konopka et al. the increase of MMP-9 level was mostly marked postsynaptically, within the dendritic spines. Moreover the activity of MMP-9 was reported in the localization corresponding with the localization of abnormal mossy fibers [10]. The authors noted that MMP-9 may exacerbate pathological processes occurring after seizures and lead to drug-resistant epilepsy.

MMP-9 as a Biomarker Associated with Epilepsy

In the research conducted so far an increased level of MMP-9 was reported in the blood serum of children who developed epileptic seizures. The increase of the MMP-9 level and the MMP-9 to TIMP-1 ratio was observed in patients with acute encephalopathy after febrile seizures, what was associated with blood-brain barrier damage. Interestingly, Brew et al. noted that the increase of MMP-9 serum level causes even greater increase of the level of TIMP-1. In children with human herpesvirus-6 (HHV-6) infection who developed seizures no significant difference in the level of MMP-9 activity was reported in comparison to infected children without coexisting seizures. In children with febrile seizures a decreased MMP-9 to TIMP-1 ratio was observed due to the TIMP-1 increase. Yet the HHV-6 infection itself caused an increase of serum MMP-9 level [13]. The authors suggested that MMP-9 level and MMP9/TIMP1 ratio might indicate central nervous system damage and development of encephalopathy.

In patients with TLE with coexisting hippocampal sclerosis an increased activity of MMP-9, an elevated MMP-9 to TIMP-1 ratio and a high level of urokinase uPAR were reported. These patients were qualified for lobectomy. After the operation a decrease of serum MMP-9 and uPAR levels was observed. Moreover, during a year after the lobectomy these patients were free from seizures. The level of MMP-9 proenzyme and activity in the tissue of epileptic focus was increased in comparison to surrounding tissues and a normal hippocampus [8].

In a varied group of patients we have recently shown a significant increase of serum MMP-9 in 1 hour and in 24 hours after seizures. The level of MMP-9 returned to control in 72 hours after seizures. The group of patients in the study consisted of patients with generalized tonic- clonic seizures, patients with convulsive and

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nonconvulsive status epilepticus, and patients with complex partial seizures. Apart from MMP-9, the levels of ICAM-1, E-selectin, and thrombomodulin were measured [14]. ICAM-1 was found to be increased only 1 hour after seizures and there were no differences in the levels of E-selectin and thrombomodulin in comparison to control group. The increase of MMP-9 and ICAM-1 was similar in all patients with epilepsy and correlated with the intensity of seizures. The results may suggest the activation of endothelium after seizures.

An increase of the MMP-9 level was found in cerebrospinal fluid of patients with bacterial meningitis who subsequently developed epileptic seizures in comparison to the patients in whom the disease was not complicated by the development of epilepsy. The result of the study suggested the role of MMP-9 in blood-brain barrier damage what was confirmed by Li et al. [11]. In their study cerebrospinal fluid was collected from the patients with a history of generalized tonic-clonic epileptic seizure. In these patients an increased level of MMP-9 was reported in comparison to control group. The increase of MMP-9 concentration correlated to blood-brain barrier damage, an increase of the albumin quotient, and the number of leukocytes in cerebrospinal fluid. An increase of the albumin quotient reflects the leakage of serum proteins to the cerebrospinal fluid and hence the blood-brain barrier permeability. In aforementioned study the increase of the MMP-9 level in cerebrospinal fluid and associated increase of blood-brain barrier permeability were reported in the period of 24 hours from the occurrence of seizures. According to the authors an increased level of MMP-9 was a marker of the influx of activated leukocytes [11].

In one of the newer studies levels of matrix metalloproteinases (among them MMP-9), oxidative stress and LDH were checked in saliva of children with epilepsy. The patients were divided into two groups on the basis of disease control: a group with well-controlled seizures and a group in which the level of control was unsatisfactory. A decrease of MMP-9 level in the saliva of all patients with epilepsy was reported and it was most significant in the patients with the unsatisfactory control of the disease. A similar decrease was noted in the levels of LDH and MMP-3 while the level of MMP-2 remained stable in all groups of patients. Additionally, the level of oxidative stress was found to be increased in the children with epilepsy. The study, apart from noting the association of the decrease in MMP-9 level in saliva with the occurrence and activity of epilepsy, also shows a possibility of noninvasive evaluation of MMP-9 level.

However, the research conducted so far suggests a possibility of evaluation of MMP- 9 as a potential marker of blood-brain barrier damage which increased concentration is associated with occurrence of epileptic seizures.

Other Potential Uses

The concept of MMP-9 as a biomarker is not new. In stroke an increase of MMP-9 is regarded to be a marker of increased blood-brain barrier permeability and hemorrhagic transformation of ischemic foci . An increase of MMP-9 has failed though as a single marker of stroke and yet a panel of biomarkers showed sensitivity and specificity on the level of approximately 90% [145, 146]. On the other hand, together with the increase of the level of natriuretic peptide type B and MMP-2 an increase of the MMP-9 concentration correlates to cardiac diseases [7]. Moreover an increased level of MMP- 9 is a predictive factor of increased mortality due to stroke and impaired healing of ulcerations associated with diabetic foot, and a MMP-9 to TIMP-1 ratio together with the level of MMP-10 is tightly correlated to severity and mortality of sepsis . In multiple sclerosis an increased level of MMP- 9 in blood serum and cerebrospinal fluid is correlated to the course of disease. Probably it may also be a predictive factor of multiple sclerosis progression. As far as neoplastic diseases are concerned high expression of MMP-9 in cancer cells is, for example, a negative prognostic factor of survival in esophageal cancer [15] whereas an increase of the level of MMP-9 in blood serum is associated with breast, pancreas, colon, and prostate cancer as well as an advanced lung cancer.

Conclusions

MMP-9 is one of the most widely met metalloproteinases in the brain. Despite its broad distribu64tion in the CNS and a huge contribution of many researchers in exploring this metalloproteinase, still many questions stay unresolved. Apart from its undoubted physiological role in the processes of cell differentiation, tissue remodeling, angiogenesis, regulation of the level and activity of cytokines and growth factors, regulation of pro- and anti-inflammatory processes, and processes leading to cell death or survival, MMP-9 also takes part in pathological processes. In epilepsy, both experimental research and clinical studies indicate that MMP-9

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contributes to formation of epileptic focus, activation of inflammation processes after the occurrence of epileptic seizures via modification of blood-brain barrier and cell death. The association between MMP-9 with drug- resistance of epilepsy has also been noticed. Yet the knowledge about MMP-9 and its role in epilepsy needs further deepening.

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