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REVIEW ARTICLE

Proteases involved in distant posttraumatic lesions: a review of literature

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ABSTRACT

Introduction. Inflammation is a state driven by pathogenic stimuli. Trauma is one of the causes of acute onset of the inflammatory pathway. Multiple proteases are capable of inducing distant multiple organ lesions (lungs, brain or spinal cord, heart, kidney, liver and systemic vessel endothelium). The onset of corresponding syndromes will complicate the clinical course of that particular patient. These molecules are potential biomarkers in trauma patients.

Material and methods. There were reviewed the PubMed, Elsevier, ResearchGate, Google Scholar, Cochrane Library, medRxiv databases using the keywords "proteases", "antiproteases" and "trauma". A total of 114 relevant sources were included. An additional74 papers were selected. Overall there 188 literature sources were reviewed.

Results and discussions. There are six classes of proteases: aspartic, glutamic, metalloproteases, cysteine, serine, and threonine proteases of which the glutamic ones are not found in mammals. Multiple processes that involve protein degradation are the fundamental mechanisms through which they mediate tissue and organ destruction after trauma-mediated inflammation. Certain inhibitors of the aforementioned proteases are of importance in these processes – they are vital in the prevention of pathophysiological processes such as fibrosis, although in the case of trauma due to their depletion there is high activity of the proteases system. The release of the protease/antiprotease system is mediated through by leukocytes, thrombocytes, myocytes and endothelium.

Conclusions. In this literature review there was described a high variety of protease and antiproteases. There is an increased complexity for the potential treatment of the distant lesions, thus the necessity for symptomatic treatment is foremost in order to diminish the lesions of the acute phase.

Keywords: protease, protease inhibitors, multiple organ failure.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

There are no broad descriptions of the protease/antiprotease system as a whole in the literature in the context of traumatic distant lesions.

The research hypothesis

There is a high myriad of proteases that are released during the systemic inflammatory response syndrome and respond with an aggressive tissue destruction in multiple tissues and organs.

The novelty added by the manuscript to the already published scientific literature

A systematic approach was chosen in this review article, thus encompassing the high versatility of the targets that need to be inhibited in the context of preventing distant lesions in trauma.

Introduction

Inflammation is a pathophysiological process that has been regarded historically in many cultures and by many researchers. The first descriptions of the inflammation were documented in the ancient Egyptian and Greek cultures. The main signs that allow us to identify inflammation are – *color*, *dolor*, *calor*, *tumor* and *functio laesa*. *Tumor* was added by Hippocrates, then Aulus Celsus added *color*, *dolor* and *calor*. Galen completed this list with the *functio laesa* [1]. The mechanisms involved in the onset of inflammation were studied in detail beginning with the second half of the 19th century. R. Virchow proposed the theory that inflammation is a "nutritional disturbance", in 1870 J. Cohnheim demonstrated that leukocyte diapedesis is present in this process, therebt proposing the vascular theory. Ten years later, C. Weigert proposed another idea – that it is a self-destruction process. In 1890, E. Metchnikoff enacted the theory that inflammation is controlled mainly by phagocytes, in accordance with Cohnheim's view. A significant shift in this field was seen in 1917, when L. Aschoff stated that inflammation is a reaction to the irritants, that may vary in different situations thus complicating the quest to define inflammation even further. Nowadays we differentiate broadly between acute and chronic inflammation [2].

After traumatic events a series of mechanisms that involve the hemostatic, endocrine and neurological systems, including immunocompetent cells act together in order to restore homeostasis [3].

In the conditions of trauma, it is important to take into account both the severity of damage and the host response. Under normal conditions, it is balanced and the inflammation remains local/limited without generalization and systemic effects. In severe trauma or polytrauma, this response leads to systemic inflammatory response syndrome (SIRS) development that occurs because of a disbalance in the pro-inflammatory and anti-inflammatory agents [4]. According to the literature, the appearance of damage-associated molecular patterns (DAMP) and inflammasomes, assembled in the immune cells, platelets and remote organs (the organs situated outside of the primary traumatic lesions), can be observed. As a result, the immune cells activated/attracted via cytokines and/or chemokines, together with increased vascular permeability and the expression of adhesion proteins on the endothelium, facilitates leukocyte diapedesis. They accumulate in injured and intact tissues. Here, these immunocompetent cells undergo degranulation and release reactive oxygen species (ROS) and a series of proteases. Consequently, "distant lesions" and sometimes multiple organ failure (MOF) develop [5]. This evolution represents an important cause of death and remains an unsolved problem in the management of critically injured patients [6].

Returning to the role of the inflammasomes in SIRS, there are a series of commonly recognized lesion sites that involve distant lesions: lungs (acute respiratory distress syndrome, ARDS), brain or spinal cord (disruption of the blood-brain and blood-medullary barriers), heart (acute coronary syndrome), liver (acute liver injury), kidneys (acute kidney injury) and the endothelium of the systemic vessels (disseminated intravascular coagulation) [5]. This concept is in accordance with the data reported in the literature. ARDS is associated with a higher level of plasma inflammatory cytokines [7], which is due to an imbalance in the protease-antiprotease system [8]. The blood-brain barrier in severe trauma had an increased permeability, as a result intracranial hemorrhage and hematomas may occur [9]. Acute coronary syndrome in polytrauma in patients with comorbidities is well recognized [10]. Acute kidney injury is mainly found in association with other injuries in severe trauma, as an indirect consequence [11]and shock associated with major trauma has been proposed to result in inadequate renal perfusion and subsequent AKI in trauma patients. This study aimed to investigate the true incidence and clinical presentation of post-traumatic AKI in hospitalized adult patients and its association with shock at a Level I trauma center. Methods: Detailed data of 78 trauma patients with AKI and 14,504 patients without AKI between January 1, 2009 and December 31, 2014 were retrieved from the Trauma Registry System. Patients with direct renal trauma were excluded from this study. Two-sided Fisher's exact or Pearson's chi-square tests were used to compare categorical data, unpaired Student's t-test was used to analyze normally distributed continuous data, and Mann-Whitney's U test was used to compare non-normally distributed data. Propensity score matching with a 1:1 ratio with logistic regression was used to evaluate the effect of shock on AKI. Results: Patients with AKI presented with significantly older age, higher incidence rates of pre-existing comorbidities, higher odds of associated injures (subdural hematoma, intracerebral hematoma, intra-abdominal injury, and hepatic injury, along with liver injuries [12]. Also, in the early stages of trauma, disseminated intravascular coagulation (DIC) is frequently reported [13-15]. All these „events" complete the pathophysiological portrait of the SIRS complications.

Taking into account the information above, the perspectives in preventing the distant lesions become clear, we propose a potential treatment or to identify the direction of the following researches in this field: usage of ROS and proteases/antiproteases as biomarkers for distant lesions in severe trauma in order to predict the outcomes for trauma patients and assess the severity of trauma.

The goal of this review was to list the elements of the protease/antiprotease system, their effects and to identify the components that can be used for the prediction of outcomes, including the secondary (indirect) lesions or the survival rate.

Material and methods

There were reviewed the PubMed, Elsevier, ResearchGate, Google Scholar, Cochrane Library, medRxiv databases using the keywords "proteases", "antiproteases" and "trauma". There were identified 114 relevant sources.

The inclusion criteria were: relevance to the topic and plausibility of statistical data in the study. Exclusion criteria were: irrelevance to the topic and low-quality statistical

data in the study. There were no inclusion/exclusion criteria pertaining to the year of publication, although sources were preferentially selected from the last 10 years in order to avoid biases outdated findings. Studies on both animal subjects and human patients studies were considered due to the scarcity of information regarding some proteases and antiproteases in the available literature.

The relevant information collected from the databases concerned the classification of proteases or antiproteases, mechanisms of action, pathological potential, clinical significance and prediction capability. Articles were selected that highlighted the potential of these molecules as biomarkers and their positive or negative effects in the context of trauma. The information was carefully studied, revised and critically structured in order to ensure an emphasis in the information structure on the objectives of this literature review.

In order to increase the validity of the information, 74 additional scientific articles were selectively reviewed. A total of 188 sources were included.

Results and discussions

The components of the protease/antiprotease system from the functional point of view can be divided into two groups: the substances that have potential negative effects (typically proteases), that are able to destroy invaders or healthy tissues, and the elements characterized by protective effects (typically antiproteases), that are able to reduce or prevent damage to the tissues.

Proteases. There are 6 main classes of proteases based on their mechanism of catalysis – aspartic, glutamic, metalloproteases, cysteine, serine, and threonine proteases, of which the glutamic class is not found in mammals [16]. Only 4 out of 6 classes are involved in trauma.

Matrix metalloproteases. A major protease class is the matrix metalloproteases, which is composed of 4 main subclasses – gelatinases, collagenases, stromelysins and elastases. Their effects are variable and are highly dependent on the microenvironment in which they act, and the multiple interactions between them and other proteases or antiproteases determine a specific pattern of expression in different conditions (tumors, necrosis or trauma).

Gelatinases

MMP-2 (Matrix metalloproteinase 2/Gelatinase A). It may be found in the granules of polymorphonuclear neutrophils [17, 18]angiogenesis and metastasis. Its remodeling is executed by a family of matrix metalloproteinases (MMPs, macrophages, monocytes, endothelial cells [19, 20], platelets [21, 22], lymphocytes [17] and astrocytes [23].

This protease has many destructive effects: it damages the basal lamina of the blood-brain barrier [17, 23], attacks the tight junctions between endothelial cells [17, 23]. Gelatinase A is able to degrade type I-V collagen, elastin and has lower proteolytic activity against proteoglycans and fibronectin [19], its activity against the type IV collagen and gelatin is notably high [24, 25].

It was highly expressed in trauma patients [26-28]in order to differentiate between a physiological tissue remodelling pattern and that associated with inflammatory tissue destruction. Methods - Analysis of SwissProt protein and EMBL/GenBank nucleotide sequence banks, protein sequence alignment, reverse transcriptase-polymerase chain reaction and nucleotide sequencing were used. Results - MMP-2 (gelatinase A, in spinal cord injury [29, 30], with elevated plasma levels after traumatic brain injury (TBI) [17] and a high level after skeletal muscle trauma in rats [19]. It was shown that it has a proaggregatory effect [31-33] and that it is a good predictor for acute respiratory distress syndrome (ARDS) [34]and involves degradation of the basement membrane. Matrix metalloproteinases (MMPs. The natural inhibitors for this protease are tissue inhibitors of metalloproteinases (TIMP 1-4) [19, 35].

MMP-9 (Matrix metalloproteinase 9/Gelatinase B). Gelatinase B may be found in the granules of the polymorphonuclear neutrophils [17, 18, 36] and lymphocytes [17]. It damages the basal lamina of the blood-brain barrier after spinal cord injury [17, 30, 37, 38], destroys the bone architecture, leading to osteoporosis [39, 40] and acts as a protease of the extracellular matrix and basal membrane (type IV collagen, gelatin, membrane growth factor receptor, tyrosine kinases and vascular endothelium adherence proteins) [32, 36, 38, 41, 42]. It is moderately expressed in trauma patients [26]in order to differentiate between a physiological tissue remodelling pattern and that associated with inflammatory tissue destruction. Methods - Analysis of SwissProt protein and EMBL/GenBank nucleotide sequence banks, protein sequence alignment, reverse transcriptase-polymerase chain reaction and nucleotide sequencing were used. Results - MMP-2 (gelatinase A, with elevated levels after burn trauma [36, 37], without predicting survivability [37], with plasma and cerebrospinal fluid levels higher in TBI before hypothermia induction [43], with increased cerebrospinal fluid (CSF) levels at the early clinical stage of TBI [17], with no difference in serum levels after a TBI [38, 41], with higher levels in case of spinal cord injury (SCI) in samples of post-mortem spinal cords detected with immunohistochemistry in rats [44] and humans [29], with higher serum levels in SCI [30], with lower levels in spinal cord injuries only after the inhibition of MMP-9 [45], with an antiaggregatory platelet effect according to a theoretical review [32] and cleaving the von Willebrand factor [46]but their physiological importance in preventing thrombus formation is unknown. This study investigated if, and which, proteases could cleave VWF in the glomerulus. The content of the glomerular basement membrane (GBM, with lower levels in ARDS along with lower MMP-9/TIMP-1 ratio values in a prospective clinical study [34]and involves degradation of the basement membrane. Matrix metalloproteinases (MMPs. Increased levels in severe sulfur mustard injuries of the eye when the tear meniscus is injured [47]. It is inhibited by TIMP 1-4 [19, 35, 36, 42, 48], melatonin, sulforaphane [30] and rutin [45].

Stromelysins

MMP-3 (Matrix metalloproteinase 3/stromelysin 1). It is found in the polymorphonuclear neutrophils [49] and chondrocytes [50, 51]. It is responsible for the degradation

of the non-collagenous extracellular matrix components and completes the collagen destruction, after it is cleaved by collagenases [49-51], it may induce seizures [52, 53]in which about 30% of patients cannot be treated adequately with anti-epileptic drugs. Brain inflammation and remodeling of the extracellular matrix (ECM the underlying mechanism being endopeptidase activity [49-51]. It is highly expressed in trauma patients [26, 54]in order to differentiate between a physiological tissue remodelling pattern and that associated with inflammatory tissue destruction. Methods - Analysis of SwissProt protein and EMBL/GenBank nucleotide sequence banks, protein sequence alignment, reverse transcriptase-polymerase chain reaction and nucleotide sequencing were used. Results - MMP-2 (gelatinase A and contributes to the lung injury as cited by a series of reviews [34, 49, 55] and has a slightly increased level after acute traumatic injuries in wounds with impaired healing [27]. It is inhibited by TIMP 1-4 [19, 35, 56, 57].

MMP-10 (Matrix metalloproteinase 10/stromelysin 2). It is found in macrophages [30, 58]. It resolves the scar tissue [58, 59], has a thrombolytic effect [60-62], stabilizes the thrombus [63]through a protease-activated receptor-1 (PAR-1, and exerts vascular remodeling effects [64]stromelysin-2 due to its promotion of the collagen lysis [30, 58]. It promotes wound healing [64]stromelysin-2 in mice [58] reported data on smoking behaviors for PLWH by gender. A slight decrease in the plasma level was observed in cases of traumatic brain injury with contusion in the first 72 hours, and a slight increase after 72 hours [65]. It is inhibited by TIMP 1-4 [19, 35, 48, 64]stromelysin-2.

MMP-11 (Matrix metalloproteinase 11/stromelysin 3). It can be found in the endothelium [66] and fibroblasts [67, 68]. It may be activated intracellularly by subtilisin-type serine proteases, due to the fact that it contains a RXK/RR furin-like recognition motif, thus having a different effect [69]. Although unable to hydrolise the extracellular matrix components, it hydrolyses the α_1-proteinase inhibitors [66, 67] and serine protease inhibitors [67], leads to the degradation of connective tissues [70, 71] due to its endopeptidase activity [66]. It is highly expressed in trauma patients [26]in order to differentiate between a physiological tissue remodelling pattern and that associated with inflammatory tissue destruction. Methods - Analysis of SwissProt protein and EMBL/GenBank nucleotide sequence banks, protein sequence alignment, reverse transcriptase-polymerase chain reaction and nucleotide sequencing were used. Results - MMP-2 (gelatinase A. It is inhibited by retinoic acid [67, 68, 72] and TIMP 1-4 [19, 35, 48].

Collagenases

MMP-1 (Matrix metalloproteinase 1/collagenase 1). It can be found in astrocytes [73], [29] and monocytes [29]. It enhances the blood-spinal cord barrier permeability, and induces macrophages and polymorphonuclear neutrophils phagocytosis signaling pathways [29, 73], causes severe cartilage damage [74]sixty rats were\nrandomly selected. Eleven rats were selected as the blank group.\nForty-four rat KOA models were established, and the remaining 5 rats\nwere used for stem cell extraction. The rats were randomly divided into\ntwo groups, and the transplantation group was treated with ADMSCs\ntransplantation. The KOA group was intragastrically administered with\nsaline. The expressions of MMP-13 mRNA and DDR2 in rats were detected by\nRT-qPCR and immunohistochemistry. Correlation analysis was performed in\nMMP-13 mRNA and DDR2 expression levels in the KOA rats. After treatment,\nthe indexes of Lequesne MG knee joints, MMP-13 mRNA and DDR2 in the\ntransplanted rats were significantly lower than those in the KOA group\n(P<0.05 because, at a neutral pH [75], it can destroy type I, II, III, V, and IX collagen [73, 76, 77] and native fibrillary collagen [76-78]. Increased levels have been reported in spinal cord trauma [29, 73], and it participates in wound healing [29, 73]. It is inhibited by TIMP 1-4 [19, 35, 48, 79]which function in extracellular matrix catabolism. Here, phage display was used to identify variants of human TIMP-2 that are selective inhibitors of human MMP-1, a collagenase whose unregulated action is linked to cancer, arthritis, and fibrosis. Using hard randomization of residues 2, 4, 5, and 6 (L1.

MMP-8 (Matrix metalloproteinase 8/Neutrophil collagenase/collagenase 2). It is found in the polymorphonuclear neutrophils [36]. It leads to the degradation of the components of the extracellular matrix [36, 80-82], may induce inflammation [81, 82], contributes to hard and soft tissue repair in mice [82], acts at neutral pH [75] as an endopeptidase [36], destroys type I, II, III, V, and IX collagen as well as native fibrillary collagen [77]. It has higher serum levels in SCI [30], and contributes to ARDS pathogenesis [34]and involves degradation of the basement membrane. Matrix metalloproteinases (MMPs, with increased levels in sepsis [81], elevated expression levels in burn trauma patients [36]. It may be inhibited by TIMP 1-4 [19, 35, 36, 48].

MMP-13 (Matrix metalloproteinase 13/collagenase 3). It can be identified in the chondrocytes [83] and fibroblasts [78]. It destroys the cartilage matrix [78, 84, 85], degrades the extracellular matrix [83, 85], leads to bone degradation [78, 86], acts at neutral pH [75] thus destroying type I, II, III, V, and IX collagen [77] as well as native fibrillary collagen [77, 78] especially type II [74, 83, 84], can bind to the platelet receptor αIIbβ3 and platelet glycoprotein (GP) VI [87]. It induces degenerative processes in cartilage and connective tissue [83], decreases platelet aggregation on collagen fibers in vascular trauma [87]. It is inhibited by MiR-320 [88, 89] and TIMP 1-4 [19, 35, 48].

Elastases

MMP-7 (Matrix metalloproteinase 7/Matrilysin). It can be identified in the macrophages [90]. It damages the extracellular matrix components [27], especially proteoglycans, insoluble elastin, and fibronectin [90], and causes synaptic reorganization in the central nervous system and excitotoxicity [91], by cleaving E-cadherin [91, 92], N-cadherin [90, 91], laminin and fibronectin [91]. Increased levels were observed after acute traumatic injury in wounds with impaired healing that are correlated with the injury severity score (ISS) [27], elevated expression was observed

ARDS [34, 92]and involves degradation of the basement membrane. Matrix metalloproteinases (MMPs, it prevents pulmonary fibrosis when it has low levels of expression [92] but increases the lung injury and fibrosis at high levels of expression [92-95]. It is inhibited by indomethacin, IL-4, IL-10, IFN-γ [96] and TIMP 1-4 [19, 35, 48].

MMP-12 (Matrix metalloproteinase 12/ Macrophage elastase/Human metalloelastase/ME). It can be identified in macrophages [58, 97]. It leads to lung structural destruction with production of mucin in the airways [35], and emphysema [98, 99]macrophage elastase-deficient (MME(- /-, it causes secondary injury processes in spinal cord injuries [30], it has protective effects in corneal injuries [100], [101] by hydrolysing the type III, IV, and V collagen, laminin-1, gelatin, proteoglycans, and elastin [35]. High concentrations that are found in trauma patients lead to extensive vascular damage, reverse repair [97], higher levels in case of SCI in samples of post-mortem spinal cords detected with immunohistochemistry [29, 30]. It can be inhibited by TIMP 1-4 [19, 35, 48].

There are also other proteases involved in trauma and have a varying serum levels following trauma. They were listed below, and grouped based on their catalytic center amino acid residue – serine, cysteine and aspartyl proteases. All of them are identified *in vivo*.

Serine proteases

Cathepsin A. It is found in the endothelium of the pulmonary capillaries [102]. It has hypotensive and immunostimulatory effects [102, 103], it may induce cardiac lesions [104, 105] and plays a major role in the oxidative stress response [105] by exerting a carboxypeptidase activity at acidic pH in the lysosome. It has deamidase and esterase activity at neutral pH [104, 106]Results: The crystal structure of mature and active cathepsin A reveals its mechanism of activation., Conclusion: Removal of a 3.3-kDa peptide (by unidentified proteases. It can metabolize endothelin-1 and angiotensin I in the bloodstream of mice [103, 104] and humans [106]Results: The crystal structure of mature and active cathepsin A reveals its mechanism of activation., Conclusion: Removal of a 3.3-kDa peptide (by unidentified proteases along with bradykinin [104]. It is inhibited by α_2 – Macroglobulin (A2MG) [107] and SAR1 [104, 108].

Cathepsin G. It may be found in the polymorphonuclear neutrophils, monocytes, macrophages and microglia [109]. It activates reactive T cells, increases cytokine and antigen-specific antibody production, increases vascular permeability which may lead to edema, and induces matrix-degrading metalloproteinases, thus leading to microvascular regression [109]. It has antimicrobial effects [110] due to its conversion of prochemerin into chemerin; it activates T cells in mice, augments antigen-specific antibody production, binds to lymphocytes including CD4+, CD8+, NK (natural killer), and B cells via a thrombin-like receptor, and increases the cytotoxicity of NK cells [109]. It activates the coagulation factor VIII *in vitro* [111] and promotes the platelet thrombus formation [112] other sources say that it cleaves this factor, thus deactivating it [46, 113, 114]but their physiological importance in preventing thrombus formation is unknown. This study investigated if, and which, proteases could cleave VWF in the glomerulus. The content of the glomerular basement membrane (GBM. Induces cardiac injury in rats [115] and mice [116]4,5-trisphosphate accumulation, activates ERK, p38 MAPK, and AKT, and decreases contractile function in cardiomyocytes. Because some cathepsin G responses mimic cardiomyocyte activation by thrombin, a role for PARs was considered. Cathepsin G markedly activates phospholipase C and p38 MAPK in cardiomyocytes from PAR-1-/- mice, but it fails to activate phospholipase C, ERK, p38 MAPK, or AKT in PAR-1- or PAR-4-expressing PAR-1-/- fibroblasts (which display robust responses to thrombin. Intensely expressed after TBI [117]. It is inhibited by serpinB1, serpinB6 [118] and secretory leucocyte protease inhibitor (SLPI) [119-121].

Trypsin. It can be found in the polymorphonuclear neutrophils [122, 123]. Has anti-inflammatory, anti-edematous, fibrinolytic, antioxidant and anti-infectious effects [124], also promotes tissue repair [124] by competing with plasmin in binding to the α_1 – antitrypsin and α_2 – macroglobulin, thus leading to an increased α_1 – antitrypsin expression and in turn this leads to an increase in the macrophage phagocytic activity, lower albumin and prealbumin loss, and higher antioxidant levels [124]. Administration of trypsin in trauma reduces the edema and ecchymosis [125], immunoreactive trypsin (IRT) serum levels are positively correlated with the ARDS manifestation in septic patients [126]. It is inhibited by α_1-antitrypsin (A1AT) [127], SLPI [119, 127], urinary trypsin inhibitor (UTI) [128], A2MG [107].

Chymotrypsin and/or chymase. Chymase is secreted by the polymorphonuclear neutrophils [129, 130], and by mast cells [121, 131]. It improves tissue repair and decreases long term proteolytic effects [124] using a mechanism that increases A1AT and A2MG expression in cells, thus increasing their activity for a period of time [124]. In trauma, it improves soft tissue regeneration [124]. It may be inhibited by α_1 – antichymotrypsin (A1ACT) [107], UTI [128], elafin [127], A2MG [107], [130] and SLPI [119, 121].

Urokinase (uPA). It may be found in polymorphonuclear neutrophils, monocytes, endothelium [132, 133]. It activates plasminogen into plasmin [132-134] due to endopeptidase-related mechanism [132-134]. Decreased levels have been reported in ARDS with acute lung injury (ALI) [134]. Increased levels of suPAR (soluble uPA receptor) in sepsis may be a predictor for ARDS [135, 136], but there it has no diagnostic value at the moment [136]. There are controversies regarding the suPAR predictive capability for mortality, some studies report a low predictive value [137], while another study reports a high predictive value [138]. Elevated plasma levels of soluble urokinase plasminogen activator receptor (suPAR) have been associated with acute kidney injury (AKI) in different clinical contexts, without having intel about their level in traumas [139]. It is inhibited by plasminogen activator type 1 inhibitor (PAI1) [132, 134] and plasminogen activator type 2 inhibitor (PAI2) [132].

HNE (Human neutrophil elastase). It is found in the polymorphonuclear neutrophils [140]. It exerts direct injury to cilia, secretory cell hyperplasia, mucin production and increases secretion in the respiratory epithelial cells [141]. In very severe cases, it leads to ARDS [140, 142, 143]. It has an antimicrobial effect [110], and mediates fibrinolysis along with degradation of plasminogen into angiostatin [144], the underlying mechanism being the proteolysis of the elastin fibers in the respiratory tract [141]. Its markedly elevated plasma levels in major trauma patients are inversely correlated with the Horowitz index [145]. It mediates acute pathogenesis in the immature brain of mice [146]. It is highly expressed in after TBI [117]. It is considered the main protease that cleaves the von Willebrand factor (vWF) [46]. It degrades the plasminogen and activates angiostatin K1, K2 and K3, which in turn lead to the shutdown of the fibrinolysis [144]. It is inhibited by elafin [143], serpinB1 [147], UTI [128], A2MG, A1AT [148] and SLPI [119].

Cysteine proteases. This class of proteases is known for its unique property of being globally inhibited by cystatins [127].

Cathepsin B. It may be found in endothelial cells, chondrocytes, synovial cells and ulceration sites [149]. It activates the trypsinogen into trypsin [150]. At an acidic pH it has peptidyl-dipeptidase and carboxypeptidase activity, at neutral-basic pH it has an endopeptidase activity [149]. The plasma levels increase in the first day after a trauma, then they fall to lower concentrations by the 3rd day and remain at the same level for 2 weeks, the increase is correlated with the injury severity, patients with sixfold increase develop multiple organ dysfunction syndrome (MODS) [149] also promotes muscular proteolysis [151]. It represents a potential biomarker, having increased concentrations in acute or subacute TBI in humans [152] and also in rodents [149]. It is inhibited by A2MG [107] and CA-074 [152].

Cathepsin C (Dipeptidyl peptidase I). It may be found in the polymorphonuclear neutrophils, cytotoxic lymphocytes, NK lymphocytes, mastocytes and reactive microglia [153]. It aggravates neuroinflammation [153] due to its protease activity [151] and by promoting the expression of proinflammatory factors such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) [153]. In trauma, it promotes muscular proteolysis [151]. It may be highly expressed in case of neuroinflammation that is determined by the central nervous system injury in mice [154]*Cat C expression and its functional role in the brain under normal conditions or in neuroinflammatory processes remain unclear. Our previous study showed that Cat C promoted the progress of brain demyelination in cuprizone-treated mice. The present study further investigated the Cat C expression and activity in lipopolysaccharide (LPS*. It is inhibited by vigdaliptin [155].

Cathepsin H. It is found in the microglial cells [156]. It promotes inflammation, leads to chronic neuroinflammation and neuronal death [156], due to its exopeptidase and endopeptidase activity at an optimal pH of 6.5-6.8 [156], above a pH of 7.0, it cannot be activated due to its precursor stability [157]. In trauma patients, it promotes muscular proteolysis [151]. It is inhibited by A2MG [107].

Cathepsin V. It may be found in macrophages [158]. It promotes tumor necrosis factor α (TNF-α) and IL-6 expression in macrophages [159] by augmenting the IL-6 and TNF-α expressions via ERK1/2 and STAT1 pathway expression [159]. In trauma patients, it induces tunica media hyperplasia, promotes monocyte adhesion to the arterial walls after vascular lesions [158]. It is inhibited by A2MG [107].

Cathepsin L. It is contained in the endothelium, and microglia [160]. It alters the microvessels integrity in focal cerebral ischemia [160] by degrading the regulatory protein perlecan and collagen IV in the microvessels [160] and contributes to the autophagocytic pathways [161]. In trauma patients it promotes muscular proteolysis [151]. It has increased concentrations after TBI [162]. It is inhibited by recombinant cathepsin L propeptide, P41 of MHC class II molecule, antimicrobial Peptide LL-37, L-kininogen, sialostatin, and cystatins A, B, C, D and F [161].

Aspartyl proteases

Cathepsin D. It can be found in the polymorphonuclear neutrophils [163]. It promotes inflammation [163] by processing various enzymes, antigens, hormones and neuropeptides (ex: C5a), intracellularly at a pH of 3-4 [163]. The plasma concentrations are significantly increased in polytrauma patients within less than one hour after trauma and remain increased for at least 48h after the incident [163]. Promotes muscular proteolysis in trauma patients [151]. It is inhibited by A2MG [107].

Antiproteases and inhibitors

α_1 – Antitrypsin (SerpinA1/A1AT). It is found in the polymorphonuclear neutrophils [164-166]leading to life-threatening multiple organ dysfunction syndrome. Previous work suggested that circulating serum factors during inflammation are critically involved in the suppression of neutrophil cell death although the identity of these antiapoptotic mediators remained elusive. In this study, we identified the acute phase protein α-1 Antitrypsin (AAT but mostly in hepatocytes [166, 167]. It ameliorates the inflammation which may lead to systemic inflammatory response syndrome (SIRS) by granting apoptosis resistance due to the prevention of PKC/Akt pathway inhibition in trauma patients [164]leading to life-threatening multiple organ dysfunction syndrome. Previous work suggested that circulating serum factors during inflammation are critically involved in the suppression of neutrophil cell death although the identity of these antiapoptotic mediators remained elusive. In this study, we identified the acute phase protein α-1 Antitrypsin (AAT. Its expression is increased in a substrate-related concentration pattern – when the substrate concentration elevates there is an increase in the expression of A1AT [124].

α_1 – Antichymotrypsin (SerpinA3). It may be found mostly in hepatocytes, and to a lesser extent in the polymorphonuclear neutrophils [167] and glial cells [168]. It has cytotoxic effects in astrocytes [169] due to the neutralisation of chymotrypsin-like proteases (chymotrypsin, cathepsin G) [167]. It may be expressed in the nervous tissue 3 hours

after a TBI and remain for 1-13 days after the event in reactive glial cells [168].

α_2 – Macroglobulin (A2MD). It can be found in chondrocytes [170] and hepatocytes [134], [170]. It slows cartilage damage in rats and humans by regulating intercellular responses [170], inhibiting almost all proteases including ADAMTS proteins [107, 130, 170]. It may inhibit exogenous proteases, regulate the clotting events along with defensins and bind to numerous cytokines as a carrier or as an inhibitor. It regulates the activity of hepcidin, leptin and neuropeptide Y, inhibits antithrombin III [130]. In trauma patients, it can bind to uPA thus inhibiting it, also it may block the activation of NF-κB pathway in ALI/ARDS [134].

MNEI (SerpinB1/Monocyte Neutrophil Elastase Inhibitor). It may be found in the polymorphonuclear neutrophils and monocytes [107, 171]. Diminishes elastase-related lung injuries [172]elastase has an antimicrobial activity and could participate in neutrophil migration, both events being critically important in host defense, explaining the controversial issue of therapeutic elastase inhibition in the setting of acute lung injury. We assessed the effect of a neutrophil elastase inhibitor, EPI-hNE-4, in single (bleomycin, 1.2 mg/rat intratracheally due to the proteolysis of elastin and chymotrypsin-like proteases [107]. In trauma patients, it can prevent the ALI/ARDS [172]elastase has an antimicrobial activity and could participate in neutrophil migration, both events being critically important in host defense, explaining the controversial issue of therapeutic elastase inhibition in the setting of acute lung injury. We assessed the effect of a neutrophil elastase inhibitor, EPI-hNE-4, in single (bleomycin, 1.2 mg/rat intratracheally.

UTI (Urinary trypsin inhibitor). It is found in human urine, may be administered as an exogenous agent [128]. It prevents apoptosis in the endothelial cells, adipocytes [128] by inhibiting the toll-like receptor 4 (TLR4) and Janus tyrosine kinase (JTK), it decreases the NF-kB, TNF-α and p53 levels in cells thus inhibiting the apoptosis cascades [128]. In traumatic patients, it prevents the manifestation of fat embolism syndrome (FES), reduces edema [128] and has beneficial effects in ARDS [173], [174, 175]. It has protective effects in astrocyte lesions after a TBI [176].

Elafin (Peptidase inhibitor 3/PI3). It may be found in monocytes [171], squamous epithelium and respiratory epithelium [177]. It has antimicrobial, antiviral, anti-inflammatory and immunomodulatory effects [178-180]elafin. It inhibits the HNE [177-180]elafin binding to its active site [181]. In traumatic patients, it is associated with ARDS development [142], further studies indicate that a polymorphism increases its likelihood [178, 180]elafin.

SLPI (Secretory Leucocyte Protease Inhibitor). It may be found in polymorphonuclear neutrophils, monocytes, macrophages [107, 177], mastocytes [121] and mucosal epithelial cells [177]. It inhibits the bacterial growth, has a neuroprotective effect in cerebral ischemia, enhances axonal regeneration in an injured central nervous system (CNS), reduces TNF-α, NF-κB and interleukin-8 (IL-8) expression [119] and has anti-inflammatory effects [177] due to the inhibition of HNE in its active site [181]. In traumatic patients, it reduces neuroinflammation, diminishes the effects of cerebral and medullar ischemia after TBI and spinal cord lesions [119]. It is not involved in ARDS development [142]. It can be cleaved and inactivated by chymase [121, 131].

TIMP-1 (Tissue inhibitor of metalloproteinase-1). It is ocated in fibroblasts [182]. It promotes oligodendrocytes differentiation [183] by receptor mediated signaling pathways [183]. It has extended expression in patients with after-burn scar tissues with elevated levels in the days 3-6 but no effect on survival predictability [37]. It is a promising biomarker for fast assessment of the total body surface area (TBSA) that is affected in burn traumas [36]. May be used for the prediction of the TBI mortality outcome on a 30 days period [38, 41].

TIMP-2 (Tissue inhibitor of metalloproteinase-2). It is located in fibroblasts [182]. It increases the wound healing rate by inhibiting the proteases [184]exudate composition and temperature in wounds to predict healing outcomes and to identify the methods that are employed to measure them. Method: A systematic review based on the outcomes of a search strategy of quantitative primary research published in the English language was conducted. Inclusion criteria limited studies to those involving in vivo and human participants with an existing or intentionally provoked wound, defined as 'a break in the epithelial integrity of the skin', and excluded in vitro and animal studies. Data synthesis and analysis was performed using structured narrative summaries of each included study arranged by concept, pH, exudate composition and temperature. The Evidence Based Literature (EBL. It has increased plasma levels in skeletal traumas [19], along with IGFBP7 may serve as an predictor for acute kidney failure [185].

TIMP-3 (Tissue inhibitor of metalloproteinase-3). It may be obtained *in vitro* from the mesenchymal stem cells. It has a neuroprotective effect in mice [186]. It plays an important role for the onset of cerebral edema after TBI. Higher concentrations lead to an increased risk of ARDS manifestation after TBI. It was proven that high doses of TIMP-3 reduce the neuroinflammation and edema followed by a TBI [187].

TIMP-4 (Tissue inhibitor of metalloproteinase-4). It is found in platelets and is involved in the activation of the pro matrix metalloproteases (pro-MMPs) besides inhibiting them. Low concentrations inhibit the platelet aggregation, high concentrations have no significant effect [188]. Possibly inhibits neovascularization. It has decreased levels in severe sulfur mustard eye injuries (SSMEI). The MMP-9/TIMP-4 ratio is decreased in SSMEI, and increases in cases when the lacrimal meniscus is also injured [47].

Conclusions

Analysis of the available literature identified the components of the protease/antiprotease system, sources/localizations, physiological and pathological effects that are potentially significant in medical practice in the post-traumatic population group and particularly regarding distant body lesions.

Based on the available information, it is not currently possible to specifically predict, prevent or treat the distant lesions due to high versatility of therapeutic targets. It may be possible to prevent the potential negative effects of the proteases and increase the potential positive effects of antiproteases in distant lesions. Moreover, a variety of potential effects of the protease/antiprotease system were identified that could explain pathophysiological processes characteristic of severe trauma.

Competing interest

None declared.

Contribution of authors

DC designed the study and revised the literature, II revised the manuscript critically, OA conceptualized the study, revised the manuscript critically and approved the final version of the manuscript.

Ethics approval

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References

1. Granger DN, Senchenkova E. Inflammation and the microcirculation. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 86 p. doi: 10.4199/C00013ED-1V01Y201006ISP008.
2. Parnes O. Inflammation. Lancet. 2008;372(9639):621. doi: 10.1016/S0140-6736(08)61262-3.
3. Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014;384(9952):1455-65. doi: 10.1016/S0140-6736(14)60687-5.
4. Osuka A, Ogura H, Ueyama M, et al. Immune response to traumatic injury: harmony and discordance of immune system homeostasis. Acute Med Surg. 2014;1(2):63-69. doi: 10.1002/ams2.17.
5. Bortolotti P, Faure E, Kipnis E. Inflammasomes in tissue damages and immune disorders after trauma. Front Immunol. 2018;9:1900. doi: 10.3389/fimmu.2018.01900.
6. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. Crit Care Clin. 2017;33(1):167-191. doi: 10.1016/j.ccc.2016.08.006.
7. Headley AS, Tolley E, Meduri GU. Infections and the inflammatory response in acute respiratory distress syndrome. Chest. 1997;111(5):1306-21. doi: 10.1378/chest.111.5.1306.
8. Acevedo J, Srinivasan M, Ponce M, et al. Protease-antiprotease imbalance in airway secretions in subjects with acute respiratory failure. Eur Respir J. 2012;40(Suppl 56):7-8.
9. McCourt R, Gould B, Kate M, et al. Blood-brain barrier compromise does not predict perihematoma edema growth in intracerebral hemorrhage. Stroke. 2015;46(4):954-60. doi: 10.1161/STROKEAHA.114.007544.
10. Joseph L, Govindarajan R, Jesudoss DS, et al. Major emergency orthopaedic surgery in patients with a concomitant acute coronary event following trauma. Int Orthop. 2019;43(8):1793-1798. doi: 10.1007/s00264-018-4163-9.
11. Lai WH, Rau CS, Wu SC, et al. Post-traumatic acute kidney injury: a cross-sectional study of trauma patients. Scand J Trauma Resusc Emerg Med. 2016;24(1):136. doi: 10.1186/s13049-016-0330-4.
12. Ramaiah SK, Jaeschke H. Role of neutrophils in the pathogenesis of acute inflammatory liver injury. Toxicol Pathol. 2007;35(6):757-66. doi: 10.1080/01926230701584163.
13. Gando S, Otomo Y. Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock. Crit Care. 2015;19(1):72. doi: 10.1186/s13054-015-0735-x.
14. Gando S. Disseminated intravascular coagulation in trauma patients. Semin Thromb Hemost. 2001;27(6):585-92. doi: 10.1055/s-2001-18864.
15. Lippi G, Cervellin G. Disseminated intravascular coagulation in trauma injuries. Semin Thromb Hemost. 2010;36(4):378-87. doi: 10.1055/s-0030-1254047.
16. López-Otín C, Bond JS. Proteases: multifunctional enzymes in life and disease. J Biol Chem. 2008;283(45):30433-7. doi: 10.1074/jbc.R800035200.
17. Grossetete M, Phelps J, Arko L, et al. Elevation of matrix metalloproteinases 3 and 9 in cerebrospinal fluid and blood in patients with severe traumatic brain injury. Neurosurgery. 2009;65(4):702-8. doi: 10.1227/01.NEU.0000351768.11363.48.
18. Gioia M, Monaco S, Van Den Steen PE, et al. The collagen binding domain of gelatinase A modulates degradation of collagen IV by gelatinase B. J Mol Biol. 2009;386(2):419-34. doi: 10.1016/j.jmb.2008.12.021.
19. Yu TS, Li Z, Zhao R, et al. Time-dependent expression of MMP-2 and TIMP-2 after rats skeletal muscle contusion and their application to determine wound age. J Forensic Sci. 2016;61(2):527-533. doi: 10.1111/1556-4029.13001.
20. Sharma R, Rosenberg A, Bennett ER, et al. A blood-based biomarker panel to risk-stratify mild traumatic brain injury. PLoS One. 2017;12(3):e0173798. doi: 10.1371/journal.pone.0173798.
21. Kuliczkowski W, Radomski M, Gąsior M, et al. MMP-2, MMP-9, and TIMP-4 and response to aspirin in diabetic and nondiabetic patients with stable coronary artery disease: a pilot study. Biomed Res Int. 2017;2017:9352015. doi: 10.1155/2017/9352015.
22. Marturano A, Hendrickx MLV, Falcinelli E, et al. Development of anti-matrix metalloproteinase-2 (MMP-2)

nanobodies as potential therapeutic and diagnostic tools. Nanomedicine. 2020;24:102103. doi: 10.1016/j.nano.2019.102103.
23. Zhang S, Kojic L, Tsang M, et al. Distinct roles for metalloproteinases during traumatic brain injury. Neurochem Int. 2016;96:46-55. doi: 10.1016/j.neuint.2016.02.013.
24. Henriet P, Emonard H. Matrix metalloproteinase-2: Not (just) a "hero" of the past. Biochimie. 2019;166:223-232. doi: 10.1016/j.biochi.2019.07.019.
25. Azhagiya Singam ER, Rajapandian V, Subramanian V. Molecular dynamics simulation study on the interaction of collagen-like peptides with gelatinase-A (MMP-2). Biopolymers. 2014;101(7):779-94. doi: 10.1002/bip.22457.
26. Konttinen YT, Ainola M, Valleala H, et al. Analysis of 16 different matrix metalloproteinases (MMP-1 to MMP-20) in the synovial membrane: different profiles in trauma and rheumatoid arthritis. Ann Rheum Dis. 1999;58(11):691-7. doi: 10.1136/ard.58.11.691.
27. Utz ER, Elster EA, Tadaki DK, et al. Metalloproteinase expression is associated with traumatic wound failure. J Surg Res. 2010;159(2):633-9. doi: 10.1016/j.jss.2009.08.021.
28. Wells JE, Rice TK, Nuttall RK, et al. An adverse role for matrix metalloproteinase 12 after spinal cord injury in mice. J Neurosci. 2003;23(31):10107-15. doi: 10.1523/JNEUROSCI.23-31-10107.2003.
29. Buss A, Pech K, Kakulas BA, et al. Matrix metalloproteinases and their inhibitors in human traumatic spinal cord injury. BMC Neurol. 2007;7:17. doi: 10.1186/1471-2377-7-17.
30. Moghaddam A, Heller R, Daniel V, et al. Exploratory study to suggest the possibility of MMP-8 and MMP-9 serum levels as early markers for remission after traumatic spinal cord injury. Spinal Cord. 2017;55(1):8-15. doi: 10.1038/sc.2016.104.
31. Sawicki G, Sanders EJ, Salas E, et al. Localization and translocation of MMP-2 during aggregation of human platelets. Thromb Haemost. 1998 Nov;80(5):836-9.
32. Santos-Martínez MJ, Medina C, Jurasz P, et al. Role of metalloproteinases in platelet function. Thromb Res. 2008;121(4):535-42. doi: 10.1016/j.thromres.2007.06.002.
33. Momi S, Falcinelli E, Giannini S, et al. Loss of matrix metalloproteinase 2 in platelets reduces arterial thrombosis in vivo. J Exp Med. 2009;206(11):2365-79. doi: 10.1084/jem.20090687.
34. Davey A, McAuley DF, O'Kane CM. Matrix metalloproteinases in acute lung injury: mediators of injury and drivers of repair. Eur Respir J. 2011;38(4):959-70. doi: 10.1183/09031936.00032111.
35. Hao W, Li M, Zhang Y, et al. Expressions of MMP-12, TIMP-4, and neutrophil elastase in PBMCs and exhaled breath condensate in patients with COPD and their relationships with disease severity and acute exacerbations. J Immunol Res. 2019;2019:7142438. doi: 10.1155/2019/7142438.
36. Hästbacka J, Fredén F, Hult M, et al. Matrix metalloproteinases -8 and -9 and tissue inhibitor of metalloproteinase-1 in burn patients. A prospective observational study. PLoS One. 2015;10(5):e0125918. doi: 10.1371/journal.pone.0125918.
37. Nagy B, Szélig L, Rendeki S, et al Dynamic changes of matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 1 after burn injury. J Crit Care. 2015;30(1):162-6. doi: 10.1016/j.jcrc.2014.07.008.
38. Lorente L, Martín MM, López P, et al. Association between serum tissue inhibitor of matrix metalloproteinase-1 levels and mortality in patients with severe brain trauma injury. PLoS One. 2014;9(4):e94370. doi: 10.1371/journal.pone.0094370.
39. Nyman JS, Lynch CC, Perrien DS, et al. Differential effects between the loss of MMP-2 and MMP-9 on structural and tissue-level properties of bone. J Bone Miner Res. 2011;26(6):1252-60. doi: 10.1002/jbmr.326.
40. Collins FL, Williams JO, Bloom AC, et al. CCL3 and MMP-9 are induced by TL1A during death receptor 3 (TNFRSF25)-dependent osteoclast function and systemic bone loss. Bone. 2017;97:94-104. doi: 10.1016/j.bone.2017.01.002.
41. Lorente L, Martín MM, Ramos L, et al. Persistently high circulating tissue inhibitor of matrix metalloproteinase-1 levels in non-survivor brain trauma injury patients. J Crit Care. 2019;51:117-121. doi: 10.1016/j.jcrc.2019.02.014.
42. Wiggins-Dohlvik K, Oakley RP, Han MS, et al. Tissue inhibitor of metalloproteinase-2 inhibits burn-induced derangements and hyperpermeability in microvascular endothelial cells. Am J Surg. 2016;211(1):197-205. doi: 10.1016/j.amjsurg.2015.08.016.
43. Suehiro E, Fujisawa H, Akimura T, et al. Increased matrix metalloproteinase-9 in blood in association with activation of interleukin-6 after traumatic brain injury: influence of hypothermic therapy. J Neurotrauma. 2004;21(12):1706-11. doi: 10.1089/neu.2004.21.1706.
44. Yu F, Kamada H, Niizuma K, et al. Induction of mmp-9 expression and endothelial injury by oxidative stress after spinal cord injury. J Neurotrauma. 2008;25(3):184-95. doi: 10.1089/neu.2007.0438.
45. Zhang P, Ma X. Effect of rutin on spinal cord injury through inhibition of the expression of MIP-2 and activation of MMP-9, and downregulation of Akt phosphorylation. Mol Med Rep. 2015;12(5):7554-60. doi: 10.3892/mmr.2015.4357.
46. Tati R, Kristoffersson AC, Manea Hedström M, et al. Neutrophil protease cleavage of von Willebrand factor in glomeruli - an anti-thrombotic mechanism in the kidney. EBioMedicine. 2017;16:302-311. doi: 10.1016/j.ebiom.2017.01.032.
47. Ghasemi H, Yaraee R, Faghihzadeh S, et al. Tear and serum MMP-9 and serum TIMPs levels in the severe sulfur mustard eye injured exposed patients. Int Im-

munopharmacol. 2019;77:105812. doi: 10.1016/j.intimp.2019.105812.
48. Sato Y, Kishi J, Suzuki K, et al. Sonic extracts from a bacterium related to periapical disease activate gelatinase A and inactivate tissue inhibitor of metalloproteinases TIMP-1 and TIMP-2. Int Endod J. 2009;42(12):1104-11. doi: 10.1111/j.1365-2591.2009.01640.x.
49. Nerusu KC, Warner RL, Bhagavathula N, et al. Matrix metalloproteinase-3 (stromelysin-1) in acute inflammatory tissue injury. Exp Mol Pathol. 2007;83(2):169-76. doi: 10.1016/j.yexmp.2007.04.003.
50. Guo L, Hao R, Tian F, et al. Interferon regulatory factor 5 (IRF5) regulates the expression of matrix metalloproteinase-3 (MMP-3) in human chondrocytes. Int Immunopharmacol. 2018;55:231-236. doi: 10.1016/j.intimp.2017.11.035.
51. Li Y, Zhao M, Xiao W. KLF15 Regulates the expression of MMP-3 in human chondrocytes. J Interferon Cytokine Res. 2018;38(8):356-362. doi: 10.1089/jir.2017.0135.
52. Korotkov A, Broekaart DWM, van Scheppingen J, et al. Increased expression of matrix metalloproteinase 3 can be attenuated by inhibition of microRNA-155 in cultured human astrocytes. J Neuroinflammation. 2018;15(1):211. doi: 10.1186/s12974-018-1245-y.
53. Wang R, Zeng GQ, Liu X, et al. Evaluation of serum matrix metalloproteinase-3 as a biomarker for diagnosis of epilepsy. J Neurol Sci. 2016;367:291-7. doi: 10.1016/j.jns.2016.06.031.
54. Lohmander LS, Roos H, Dahlberg L, et al. Temporal patterns of stromelysin-1, tissue inhibitor, and proteoglycan fragments in human knee joint fluid after injury to the cruciate ligament or meniscus. J Orthop Res. 1994;12(1):21-8. doi: 10.1002/jor.1100120104.
55. Craig VJ, Zhang L, Hagood JS, et al. Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol. 2015;53(5):585-600. doi: 10.1165/rcmb.2015-0020TR.
56. Heuschkel R, MacDonald TT, Monteleone G, et al. Imbalance of stromelysin-1 and timp-1 mrna and protein in the mucosal lesions of children with inflammatory bowel disease. Gut. 2000 Jul;47(1):57-62. doi: 10.1136/gut.47.1.57.
57. Nagase H, Suzuki K, Cawston TE, et al. Involvement of a region near valine-69 of tissue inhibitor of metalloproteinases (TIMP)-1 in the interaction with matrix metalloproteinase 3 (stromelysin 1). Biochem J. 1997;325 (Pt 1)(Pt 1):163-7. doi: 10.1042/bj3250163.
58. McMahan RS, Birkland TP, Smigiel KS, et al. Stromelysin-2 (MMP10) moderates inflammation by controlling macrophage activation. J Immunol. 2016;197(3):899-909. doi: 10.4049/jimmunol.1600502.
59. Rohani MG, McMahan RS, Razumova MV, et al. MMP-10 regulates collagenolytic activity of alternatively activated resident macrophages. J Invest Dermatol. 2015;135(10):2377-2384. doi: 10.1038/jid.2015.167.
60. Orbe J, Barrenetxe J, Rodriguez JA, et al. Matrix metalloproteinase-10 effectively reduces infarct size in experimental stroke by enhancing fibrinolysis via a thrombin-activatable fibrinolysis inhibitor-mediated mechanism. Circulation. 2011;124(25):2909-19. doi: 10.1161/CIRCULATIONAHA.111.047100.
61. Roncal C, Martinez de Lizarrondo S, Salicio A, et al. New thrombolytic strategy providing neuroprotection in experimental ischemic stroke: MMP10 alone or in combination with tissue-type plasminogen activator. Cardiovasc Res. 2017;113(10):1219-1229. doi: 10.1093/cvr/cvx069.
62. Navarro-Oviedo M, Roncal C, Salicio A, et al. MMP10 promotes efficient thrombolysis after ischemic stroke in mice with induced diabetes. Transl Stroke Res. 2019;10(4):389-401. doi: 10.1007/s12975-018-0652-9.
63. Orbe J, Rodríguez JA, Calvayrac O, et al. Matrix metalloproteinase-10 is upregulated by thrombin in endothelial cells and increased in patients with enhanced thrombin generation. Arterioscler Thromb Vasc Biol. 2009;29(12):2109-16. doi: 10.1161/ATVBAHA.109.194589.
64. Batra J, Robinson J, Soares AS, et al. Matrix metalloproteinase-10 (MMP-10) interaction with tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2: binding studies and crystal structure. J Biol Chem. 2012;287(19):15935-46. doi: 10.1074/jbc.M112.341156.
65. Guilfoyle MR, Carpenter KL, Helmy A, et al. Matrix metalloproteinase expression in contusional traumatic brain injury: a paired microdialysis study. J Neurotrauma. 2015;32(20):1553-9. doi: 10.1089/neu.2014.3764.
66. Lijnen HR, Van Hoef B, Vanlinthout I, et al. Accelerated neointima formation after vascular injury in mice with stromelysin-3 (MMP-11) gene inactivation. Arterioscler Thromb Vasc Biol. 1999;19(12):2863-70. doi: 10.1161/01.atv.19.12.2863.
67. Anderson IC, Sugarbaker DJ, Ganju RK, et al. Stromelysin-3 is overexpressed by stromal elements in primary non-small cell lung cancers and regulated by retinoic acid in pulmonary fibroblasts. Cancer Res. 1995;55(18):4120-6.
68. Guérin E, Ludwig MG, Basset P, et al. Stromelysin-3 induction and interstitial collagenase repression by retinoic acid. Therapeutical implication of receptor-selective retinoids dissociating transactivation and AP-1-mediated transrepression. J Biol Chem. 1997;272(17):11088-95. doi: 10.1074/jbc.272.17.11088.
69. Zhang H, Adwanikar H, Werb Z, et al. Matrix metalloproteinases and neurotrauma: evolving roles in injury and reparative processes. Neuroscientist. 2010;16(2):156-70. doi: 10.1177/1073858409355830.
70. Lee J, Lee J, Kim JH. Identification of matrix metalloproteinase 11 as a prognostic biomarker in pancreatic

cancer. Anticancer Res. 2019;39(11):5963-5971. doi: 10.21873/anticanres.13801.
71. Rickaby R, El Khoury LY, Samiric T, et al. Epigenetic status of the human *MMP11* gene promoter is altered in patellar tendinopathy. J Sports Sci Med. 2019;18(1):155-159.
72. von Marschall Z, Riecken EO, Rosewicz S. Stromelysin 3 is overexpressed in human pancreatic carcinoma and regulated by retinoic acid in pancreatic carcinoma cell lines. Gut. 1998;43(5):692-8. doi: 10.1136/gut.43.5.692.
73. Zhou Y, Cui Z, Xia X, et al. Matrix metalloproteinase-1 (MMP-1) expression in rat spinal cord injury model. Cell Mol Neurobiol. 2014;34(8):1151-63. doi: 10.1007/s10571-014-0090-5.
74. Li J, Zhu X, Shao Q, et al. Allogeneic adipose-derived stem cell transplantation on knee osteoarthritis rats and its effect on MMP-13 and DDR2. Exp Ther Med. 2019;18(1):99-104. doi: 10.3892/etm.2019.7554.
75. Inada M, Wang Y, Byrne MH, et al. Critical roles for collagenase-3 (Mmp13) in development of growth plate cartilage and in endochondral ossification. Proc Natl Acad Sci USA. 2004;101(49):17192-7. doi: 10.1073/pnas.0407788101.
76. Ma Y, Iyer R, Bras L, et al. Cross talk between inflammation and extracellular matrix following myocardial infarction. In: Blankesteijn WM, Altara R, editors. Inflammation in heart failure. Amsterdam: Elsevier/Academic Press; 2015. p. 67-79. doi: 10.1016/B978-0-12-800039-7.00004-9.
77. Inanc S, Keles D, Oktay G. An improved collagen zymography approach for evaluating the collagenases MMP-1, MMP-8, and MMP-13. Biotechniques. 2017;63(4):174-180. doi: 10.2144/000114597.
78. Agere SA, Akhtar N, Watson JM, et al. RANTES/CCL5 induces collagen degradation by activating MMP-1 and MMP-13 expression in human rheumatoid arthritis synovial fibroblasts. Front Immunol. 2017;8:1341. doi: 10.3389/fimmu.2017.01341.
79. Bahudhanapati H, Zhang Y, Sidhu SS, et al. Phage display of tissue inhibitor of metalloproteinases-2 (TIMP-2): identification of selective inhibitors of collagenase-1 (metalloproteinase 1 (MMP-1)). J Biol Chem. 2011;286(36):31761-70. doi: 10.1074/jbc.M111.253328.
80. Nwomeh BC, Liang HX, Cohen IK, et al. MMP-8 is the predominant collagenase in healing wounds and nonhealing ulcers. J Surg Res. 1999;81(2):189-95. doi: 10.1006/jsre.1998.5495.
81. Daly MC, Atkinson SJ, Varisco BM, et al. Role of matrix metalloproteinase-8 as a mediator of injury in intestinal ischemia and reperfusion. FASEB J. 2016;30(10):3453-3460. doi: 10.1096/fj.201600242R.
82. Astrom P. Regulatory mechanisms mediating matrix metalloproteinase-8 effects in oral tissue repair and tongue cancer [dissertation]. Oulu (FI): University of Oulu; 2014.
83. Otero M, Plumb DA, Tsuchimochi K, et al. E74-like factor 3 (ELF3) impacts on matrix metalloproteinase 13 (MMP13) transcriptional control in articular chondrocytes under proinflammatory stress. J Biol Chem. 2012;287(5):3559-72. doi: 10.1074/jbc.M111.265744.
84. Yang Q, Ding W, Cao Y, et al. Interferonregulatory-factor-8(IRF-8) regulates the expression of matrix metalloproteinase-13 (MMP-13) in chondrocytes. Cell Stress Chaperones. 2018;23(3):393-398. doi: 10.1007/s12192-017-0849-y.
85. Li H, Wang D, Yuan Y, et al. New insights on the MMP-13 regulatory network in the pathogenesis of early osteoarthritis. Arthritis Res Ther. 2017;19(1):248. doi: 10.1186/s13075-017-1454-2.
86. Li J, Liao EY, Dai RC, et al. Effects of 17 beta-estradiol on the expression of interstitial collagenases-8 and -13 (MMP-8 and MMP-13) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in ovariectomized rat osteoblastic cells. J Mol Histol. 2004;35(8-9):723-31. doi: 10.1007/s10735-004-6206-3.
87. Howes JM, Pugh N, Hamaia SW, et al. MMP-13 binds to platelet receptors αIIbβ3 and GPVI and impairs aggregation and thrombus formation. Res Pract Thromb Haemost. 2018;2(2):370-379. doi: 10.1002/rth2.12088.
88. Zhang HX, Sun C, Yu HC, et al. Targeted inhibition of β-catenin by miR-320 and decreased MMP-13 expression in suppressing chondrocyte collagen degradation. Eur Rev Med Pharmacol Sci. 2018 Sep;22(18):5828-5835. doi: 10.26355/eurrev_201809_15909.
89. Meng F, Zhang Z, Chen W, et al. MicroRNA-320 regulates matrix metalloproteinase-13 expression in chondrogenesis and interleukin-1β-induced chondrocyte responses. Osteoarthritis Cartilage. 2016;24(5):932-41. doi: 10.1016/j.joca.2015.12.012.
90. Halpert I, Sires UI, Roby JD, et al. Matrilysin is expressed by lipid-laden macrophages at sites of potential rupture in atherosclerotic lesions and localizes to areas of versican deposition, a proteoglycan substrate for the enzyme. Proc Natl Acad Sci USA. 1996;93(18):9748-53. doi: 10.1073/pnas.93.18.9748.
91. Bilousova TV, Rusakov DA, Ethell DW, et al. Matrix metalloproteinase-7 disrupts dendritic spines in hippocampal neurons through NMDA receptor activation. J Neurochem. 2006;97(1):44-56. doi: 10.1111/j.1471-4159.2006.03701.x.
92. Manicone AM, Huizar I, McGuire JK. Matrilysin (Matrix Metalloproteinase-7) regulates anti-inflammatory and antifibrotic pulmonary dendritic cells that express CD103 (alpha(E)beta(7)-integrin). Am J Pathol. 2009;175(6):2319-31. doi: 10.2353/ajpath.2009.090101.
93. Villar J, Cabrera-Benítez NE, Ramos-Nuez A, et al. Early activation of pro-fibrotic WNT5A in sepsis-induced acute lung injury. Crit Care. 2014;18(5):568. doi: 10.1186/s13054-014-0568-z.

94. Raish M, Ahmad A, Ahmad Ansari M, et al. Sinapic acid ameliorates bleomycin-induced lung fibrosis in rats. Biomed Pharmacother. 2018;108:224-231. doi: 10.1016/j.biopha.2018.09.032.
95. Zuo F, Kaminski N, Eugui E, et al. Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. Proc Natl Acad Sci USA. 2002;99(9):6292-7. doi: 10.1073/pnas.092134099.
96. Busiek DF, Baragi V, Nehring LC, et al. Matrilysin expression by human mononuclear phagocytes and its regulation by cytokines and hormones. J Immunol. 1995;154(12):6484-91.
97. Aristorena M, Gallardo-Vara E, Vicen M, et al. MMP-12, secreted by pro-inflammatory macrophages, targets endoglin in human macrophages and endothelial cells. Int J Mol Sci. 2019;20(12):3107. doi: 10.3390/ijms20123107.
98. Hautamaki RD, Kobayashi DK, Senior RM, et al. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science. 1997;277(5334):2002-4. doi: 10.1126/science.277.5334.2002.
99. Churg A, Zhou S, Wright JL. Series "matrix metalloproteinases in lung health and disease": matrix metalloproteinases in COPD. Eur Respir J. 2012;39(1):197-209. doi: 10.1183/09031936.00121611.
100. Wolf M, Maltseva I, Clay SM, et al. Effects of MMP12 on cell motility and inflammation during corneal epithelial repair. Exp Eye Res. 2017;160:11-20. doi: 10.1016/j.exer.2017.04.007.
101. Chan MF, Li J, Bertrand A, et al. Protective effects of matrix metalloproteinase-12 following corneal injury. J Cell Sci. 2013;126(Pt 17):3948-60. doi: 10.1242/jcs.128033.
102. Hyun SW, Liu A, Liu Z, et al. The NEU1-selective sialidase inhibitor, C9-butyl-amide-DANA, blocks sialidase activity and NEU1-mediated bioactivities in human lung in vitro and murine lung in vivo. Glycobiology. 2016;26(8):834-49. doi: 10.1093/glycob/cww060.
103. Pan X, Grigoryeva L, Seyrantepe V, et al. Serine carboxypeptidase SCPEP1 and cathepsin A play complementary roles in regulation of vasoconstriction via inactivation of endothelin-1. PLoS Genet. 2014;10(2):e1004146. doi: 10.1371/journal.pgen.1004146.
104. Petrera A, Gassenhuber J, Ruf S, et al. Cathepsin A inhibition attenuates myocardial infarction-induced heart failure on the functional and proteomic levels. J Transl Med. 2016;14(1):153. doi: 10.1186/s12967-016-0907-8.
105. Petrera A, Kern U, Linz D, et al. Proteomic profiling of cardiomyocyte-specific cathepsin A overexpression links cathepsin A to the oxidative stress response. J Proteome Res. 2016;15(9):3188-95. doi: 10.1021/acs.jproteome.6b00413.
106. Kolli N, Garman SC. Proteolytic activation of human cathepsin A. J Biol Chem. 2014;289(17):11592-11600. doi: 10.1074/jbc.M113.524280.
107. Korkmaz B, Horwitz MS, Jenne DE, et al. Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human diseases. Pharmacol Rev. 2010;62(4):726-59. doi: 10.1124/pr.110.002733.
108. Tillner J, Lehmann A, Paehler T, et al. Tolerability, safety, and pharmacokinetics of the novel cathepsin A inhibitor SAR164653 in healthy subjects. Clin Pharmacol Drug Dev. 2016;5(1):57-68. doi: 10.1002/cpdd.201.
109. Gao S, Zhu H, Zuo X, et al. Cathepsin G and its role in inflammation and autoimmune diseases. Arch Rheumatol. 2018;33(4):498-504. doi: 10.5606/ArchRheumatol.2018.6595.
110. Campanelli D, Detmers PA, Nathan CF, et al. Azurocidin and a homologous serine protease from neutrophils. Differential antimicrobial and proteolytic properties. J Clin Invest. 1990;85(3):904-15. doi: 10.1172/JCI114518.
111. Gale AJ, Rozenshteyn D. Cathepsin G, a leukocyte protease, activates coagulation factor VIII. Thromb Haemost. 2008;99(1):44-51. doi: 10.1160/TH07-08-0495.
112. Faraday N, Schunke K, Saleem S, et al. Cathepsin G-dependent modulation of platelet thrombus formation in vivo by blood neutrophils. PLoS One. 2013;8(8):e71447. doi: 10.1371/journal.pone.0071447.
113. Lancellotti S, Basso M, De Cristofaro R. Proteolytic processing of von Willebrand factor by adamts13 and leukocyte proteases. Mediterr J Hematol Infect Dis. 2013;5(1):e2013058. doi: 10.4084/MJHID.2013.058.
114. Raife TJ, Cao W, Atkinson BS, et al. Leukocyte proteases cleave von Willebrand factor at or near the ADAMTS13 cleavage site. Blood. 2009;114(8):1666-74. doi: 10.1182/blood-2009-01-195461.
115. Miller SA, Kolpakov MA, Guo X, et al. Intracardiac administration of neutrophil protease cathepsin G activates noncanonical inflammasome pathway and promotes inflammation and pathological remodeling in non-injured heart. J Mol Cell Cardiol. 2019;134:29-39. doi: 10.1016/j.yjmcc.2019.06.016.
116. Sabri A, Alcott SG, Elouardighi H, et al. Neutrophil cathepsin G promotes detachment-induced cardiomyocyte apoptosis via a protease-activated receptor-independent mechanism. J Biol Chem. 2003;278(26):23944-54. doi: 10.1074/jbc.M302718200.
117. Bank U, Reinhold D, Schneemilch C, et al. Selective proteolytic cleavage of IL-2 receptor and IL-6 receptor ligand binding chains by neutrophil-derived serine proteases at foci of inflammation. J Interferon Cytokine Res. 1999;19(11):1277-87. doi: 10.1089/107999099312957.
118. Burgener SS, Leborgne NGF, Snipas SJ, et al. Cathepsin G inhibition by Serpinb1 and Serpinb6 prevents

programmed necrosis in neutrophils and monocytes and reduces GSDMD-driven inflammation. Cell Rep. 2019;27(12):3646-3656.e5. doi: 10.1016/j.celrep.2019.05.065.
119. Hannila SS. Secretory leukocyte protease inhibitor (SLPI): emerging roles in CNS trauma and repair. Neuroscientist. 2015;21(6):630-6. doi: 10.1177/1073858414546000.
120. Renesto P, Balloy V, Kamimura T, et al. Inhibition by recombinant SLPI and half-SLPI (Asn55-Ala107) of elastase and cathepsin G activities: consequence for neutrophil-platelet cooperation. Br J Pharmacol. 1993;108(4):1100-6. doi: 10.1111/j.1476-5381.1993.tb13511.x.
121. Belkowski SM, Masucci J, Mahan A, et al. Cleaved SLPI, a novel biomarker of chymase activity. Biol Chem. 2008;389(9):1219-24. doi: 10.1515/BC.2008.138.
122. Merza M, Hartman H, Rahman M, et al. Neutrophil extracellular traps induce trypsin activation, inflammation, and tissue damage in mice with severe acute pancreatitis. Gastroenterology. 2015;149(7):1920-1931.e8. doi: 10.1053/j.gastro.2015.08.026.
123. Yang ZW, Meng XX, Xu P. Central role of neutrophil in the pathogenesis of severe acute pancreatitis. J Cell Mol Med. 2015;19(11):2513-20. doi: 10.1111/jcmm.12639.
124. Shah D, Mital K. The Role of trypsin:chymotrypsin in tissue repair. Adv Ther. 2018;35(1):31-42. doi: 10.1007/s12325-017-0648-y.
125. Miller RR, De Young DV, Paxinos J. Enzymes for trauma. Postgrad Med J. 1970;46(533):154-6. doi: 10.1136/pgmj.46.533.154.
126. Deby-Dupont G, Haas M, Pincemail J, et al. Immunoreactive trypsin in the adult respiratory distress syndrome. Intensive Care Med. 1984;10(1):7-12. doi: 10.1007/BF00258062.
127. Greene CM, McElvaney NG. Proteases and antiproteases in chronic neutrophilic lung disease - relevance to drug discovery. Br J Pharmacol. 2009;158(4):1048-58. doi: 10.1111/j.1476-5381.2009.00448.x.
128. Xiong L, Sun L, Liu S, et al. The protective roles of urinary trypsin inhibitor in brain injury following fat embolism syndrome in a rat model. Cell Transplant. 2019;28(6):704-712. doi: 10.1177/0963689718814766.
129. Venge P. Kinetic studies of cell migration in a modified Boyden chamber: dependence on cell concentration and effects of the chymotrypsin-like cationic protein of human granulocytes. J Immunol. 1979;122(4):1180-4.
130. Rehman AA, Ahsan H, Khan FH. α-2-Macroglobulin: a physiological guardian. J Cell Physiol. 2013;228(8):1665-75. doi: 10.1002/jcp.24266.
131. Thorpe M, Yu J, Boinapally V, et al. Extended cleavage specificity of the mast cell chymase from the crab-eating macaque (Macaca fascicularis): an interesting animal model for the analysis of the function of the human mast cell chymase. Int Immunol. 2012;24(12):771-82. doi: 10.1093/intimm/dxs081.
132. Mahmood N, Mihalcioiu C, Rabbani SA. Multifaceted role of the urokinase-type plasminogen activator (uPA) and its receptor (uPAR): diagnostic, prognostic, and therapeutic applications. Front Oncol. 2018;8:24. doi: 10.3389/fonc.2018.00024.
133. Sanderson-Smith ML, Zhang Y, Ly D, et al. A key role for the urokinase plasminogen activator (uPA) in invasive Group A streptococcal infection. PLoS Pathog. 2013;9(7):e1003469. doi: 10.1371/journal.ppat.1003469.
134. Komissarov AA, Stankowska D, Krupa A, et al. Novel aspects of urokinase function in the injured lung: role of α2-macroglobulin. Am J Physiol Lung Cell Mol Physiol. 2012;303(12):L1037-45. doi: 10.1152/ajplung.00117.2012.
135. Chen D, Wu X, Yang J, et al. Serum plasminogen activator urokinase receptor predicts elevated risk of acute respiratory distress syndrome in patients with sepsis and is positively associated with disease severity, inflammation and mortality. Exp Ther Med. 2019;18(4):2984-2992. doi: 10.3892/etm.2019.7931.
136. Shan L, Shan F, Li J, et al. Association of circulating suPAR with disease severity and clinical outcomes in patients with ARDS induced by intra-abdominal infections: a prospective observational study. Int J Clin Exp Med. 2016;9(7):12788-12795.
137. Geboers DG, de Beer FM, Tuip-de Boer AM, et al. Plasma suPAR as a prognostic biological marker for ICU mortality in ARDS patients. Intensive Care Med. 2015;41(7):1281-90. doi: 10.1007/s00134-015-3924-9.
138. Jalkanen V, Yang R, Linko R, et al. SuPAR and PAI-1 in critically ill, mechanically ventilated patients. Intensive Care Med. 2013;39(3):489-96. doi: 10.1007/s00134-012-2730-x.
139. Hayek SS, Leaf DE, Samman Tahhan A, et al. Soluble urokinase receptor and acute kidney injury. N Engl J Med. 2020;382(5):416-426. doi: 10.1056/NEJMoa1911481.
140. Bhatia R, Dent C, Topley N, et al. Neutrophil priming for elastase release in adult blunt trauma patients. J Trauma. 2006;60(3):590-6. doi: 10.1097/01.ta.0000205614.51885.ff.
141. Brusselle GG, Van Braeckel E. Sputum neutrophil elastase as a biomarker for disease activity in bronchiectasis. Am J Respir Crit Care Med. 2017;195(10):1289-1291. doi: 10.1164/rccm.201612-2476ED.
142. Wang Z, Chen F, Zhai R, et al. Plasma neutrophil elastase and elafin imbalance is associated with acute respiratory distress syndrome (ARDS) development. PLoS One. 2009;4(2):e4380. doi: 10.1371/journal.pone.0004380.
143. Wang T, Zhu Z, Liu Z, et al. Plasma neutrophil

elastase and elafin as prognostic biomarker for acute respiratory distress syndrome: a multicenter survival and longitudinal prospective observation study. Shock. 2017;48(2):168-174. doi: 10.1097/SHK.0000000000000845.
144. Barrett CD, Moore HB, Banerjee A, et al. Human neutrophil elastase mediates fibrinolysis shutdown through competitive degradation of plasminogen and generation of angiostatin. J Trauma Acute Care Surg. 2017;83(6):1053-1061. doi: 10.1097/TA.0000000000001685.
145. Donnelly SC, MacGregor I, Zamani A, et al. Plasma elastase levels and the development of the adult respiratory distress syndrome. Am J Respir Crit Care Med. 1995;151(5):1428-33. doi: 10.1164/ajrccm.151.5.7735596.
146. Semple BD, Trivedi A, Gimlin K, et al. Neutrophil elastase mediates acute pathogenesis and is a determinant of long-term behavioral recovery after traumatic injury to the immature brain. Neurobiol Dis. 2015;74:263-80. doi: 10.1016/j.nbd.2014.12.003.
147. Uchiyama K, Naito Y, Takagi T, et al. Serpin B1 protects colonic epithelial cell via blockage of neutrophil elastase activity and its expression is enhanced in patients with ulcerative colitis. Am J Physiol Gastrointest Liver Physiol. 2012;302(10):G1163-70. doi: 10.1152/ajpgi.00292.2011.
148. Kunder M, Lakshmaiah V, Moideen Kutty AV. Plasma neutrophil elastase, α_1-antitrypsin, α_2-macroglobulin and neutrophil elastase-α_1-antitrypsin complex levels in patients with dengue fever. Indian J Clin Biochem. 2018;33(2):218-221. doi: 10.1007/s12291-017-0658-1.
149. Hook G, Jacobsen JS, Grabstein K, et al. Cathepsin B is a new drug target for traumatic brain injury therapeutics: evidence for E64d as a promising lead drug candidate. Front Neurol. 2015;6:178. doi: 10.3389/fneur.2015.00178.
150. Talukdar R, Sareen A, Zhu H, et al. Release of cathepsin B in cytosol causes cell death in acute pancreatitis. Gastroenterology. 2016;151(4):747-758.e5. doi: 10.1053/j.gastro.2016.06.042.
151. Farges MC, Balcerzak D, Fisher BD, et al. Increased muscle proteolysis after local trauma mainly reflects macrophage-associated lysosomal proteolysis. Am J Physiol Endocrinol Metab. 2002;282(2):E326-35. doi: 10.1152/ajpendo.00345.2001.
152. Boutté AM, Hook V, Thangavelu B, et al. Penetrating traumatic brain injury triggers dysregulation of cathepsin B protein levels independent of cysteine protease activity in brain and cerebral spinal fluid. J Neurotrauma. 2020;37(13):1574-1586. doi: 10.1089/neu.2019.6537.
153. Liu Q, Zhang Y, Liu S, et al. Cathepsin C promotes microglia M1 polarization and aggravates neuroinflammation via activation of Ca^{2+}-dependent PKC/p38MAPK/NF-κB pathway. J Neuroinflammation. 2019;16(1):10. doi: 10.1186/s12974-019-1398-3.
154. Fan K, Wu X, Fan B, et al. Up-regulation of microglial cathepsin C expression and activity in lipopolysaccharide-induced neuroinflammation. J Neuroinflammation. 2012;9:96. doi: 10.1186/1742-2094-9-96.
155. Laine DI, Busch-Petersen J. Inhibitors of cathepsin C (dipeptidyl peptidase I). Expert Opin Ther Pat. 2010;20(4):497-506. doi: 10.1517/13543771003657172.
156. Fan K, Li D, Zhang Y, et al. The induction of neuronal death by up-regulated microglial cathepsin H in LPS-induced neuroinflammation. J Neuroinflammation. 2015;12:54. doi: 10.1186/s12974-015-0268-x.
157. Kirschke H. Cathepsin H. In: Rawlings ND, Salvesen G, editors. Handbook proteolytic enzymes. 3rd ed. Amsterdam: Elsevier/Academic Press; 2013. p. 1795-1800.
158. Cai J, Zhong H, Wu J, et al. Cathepsin L promotes vascular intimal hyperplasia after arterial injury. Mol Med. 2017;23:92-100. doi: 10.2119/molmed.2016.00222.
159. Leng YP, Ma YS, Li XG, et al. l-Homocysteine-induced cathepsin V mediates the vascular endothelial inflammation in hyperhomocysteinaemia. Br J Pharmacol. 2018;175(8):1157-1172. doi: 10.1111/bph.13920.
160. Gu YH, Kanazawa M, Hung SY, et al. Cathepsin L acutely alters microvessel integrity within the neurovascular unit during focal cerebral ischemia. J Cereb Blood Flow Metab. 2015;35(11):1888-900. doi: 10.1038/jcbfm.2015.170.
161. Dana D, Pathak SK. A Review of small molecule inhibitors and functional probes of human cathepsin L. Molecules. 2020;25(3):698. doi: 10.3390/molecules25030698.
162. Kanbak G, Kartkaya K, Ozcelik E, et al. The neuroprotective effect of acute moderate alcohol consumption on caspase-3 mediated neuroapoptosis in traumatic brain injury: the role of lysosomal cathepsin L and nitric oxide. Gene. 2013;512(2):492-5. doi: 10.1016/j.gene.2012.10.012.
163. Huber-Lang M, Denk S, Fulda S, et al. Cathepsin D is released after severe tissue trauma in vivo and is capable of generating C5a in vitro. Mol Immunol. 2012;50(1-2):60-5. doi: 10.1016/j.molimm.2011.12.005.
164. Sarabhai T, Peter C, Bär AK, et al. Serum α-1 Antitrypsin (AAT) antagonizes intrinsic apoptosis induction in neutrophils from patients with systemic inflammatory response syndrome. PLoS One. 2017;12(5):e0177450. doi: 10.1371/journal.pone.0177450.
165. Chapman KR, Chorostowska-Wynimko J, Koczulla AR, et al. Alpha 1 antitrypsin to treat lung disease in alpha 1 antitrypsin deficiency: recent developments and clinical implications. Int J Chron Obstruct Pulmon Dis. 2018;13:419-432. doi: 10.2147/COPD.S149429.
166. Chiuchiolo MJ, Crystal RG. Gene Therapy for alpha-1 antitrypsin deficiency lung disease. Ann Am Thorac

Soc. 2016;13 Suppl 4:S352-69. doi: 10.1513/AnnalsATS.201506-344KV.
167. Bergman D, Kadner SS, Cruz MR, et al. Synthesis of alpha 1-antichymotrypsin and alpha 1-antitrypsin by human trophoblast. Pediatr Res. 1993;34(3):312-7. doi: 10.1203/00006450-199309000-00015.
168. Hausmann R, Betz P. Course of glial immunoreactivity for vimentin, tenascin and alpha1-antichymotrypsin after traumatic injury to human brain. Int J Legal Med. 2001;114(6):338-42. doi: 10.1007/s004140000199.
169. Park J, Masaki T, Mezaki Y, et al. Alpha-1 antichymotrypsin is involved in astrocyte injury in concert with arginine-vasopressin during the development of acute hepatic encephalopathy. PLoS One. 2017;12(12):e0189346. doi: 10.1371/journal.pone.0189346.
170. Wang S, Wei X, Zhou J, et al. Identification of α2-macroglobulin as a master inhibitor of cartilage-degrading factors that attenuates the progression of posttraumatic osteoarthritis. Arthritis Rheumatol. 2014;66(7):1843-53. doi: 10.1002/art.38576.
171. Jenne DE. Structure of the azurocidin, proteinase 3, and neutrophil elastase genes. Implications for inflammation and vasculitis. Am J Respir Crit Care Med. 1994;150(6 Pt 2):S147-54. doi: 10.1164/ajrccm/150.6_Pt_2.S147.
172. Honoré S, Attalah HL, Azoulay E, et al. Beneficial effect of an inhibitor of leukocyte elastase (EPI-hNE-4) in presence of repeated lung injuries. Shock. 2004;22(2):131-6. doi: 10.1097/01.shk.0000126861.77543.d0.
173. Zhang X, Zhu Z, Jiao W, et al. Ulinastatin treatment for acute respiratory distress syndrome in China: a meta-analysis of randomized controlled trials. BMC Pulm Med. 2019;19(1):196. doi: 10.1186/s12890-019-0968-6.
174. Leng YX, Yang SG, Song YH, et al. Ulinastatin for acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. World J Crit Care Med. 2014;3(1):34-41. doi: 10.5492/wjccm.v3.i1.34.
175. He G, Li Q, Li W, et al. Effect of ulinastatin on interleukins and pulmonary function in bypass patients: a meta-analysis of randomized controlled trials. Herz. 2020;45(4):335-346. doi: 10.1007/s00059-018-4732-0.
176. Zhang S, Yu R, Zhang Y, et al. Cytoprotective effects of urinary trypsin inhibitor on astrocytes injured by sustained compression. Mol Biol Rep. 2014;41(3):1311-6. doi: 10.1007/s11033-013-2976-6.
177. Williams SE, Brown TI, Roghanian A, et al. SLPI and elafin: one glove, many fingers. Clin Sci (Lond). 2006;110(1):21-35. doi: 10.1042/CS20050115.
178. Tejera P, Wang Z, Zhai R, et al. Genetic polymorphisms of peptidase inhibitor 3 (elafin) are associated with acute respiratory distress syndrome. Am J Respir Cell Mol Biol. 2009;41(6):696-704. doi: 10.1165/rcmb.2008-0410OC.
179. Wang Z, Beach D, Su L, et al. A genome-wide expression analysis in blood identifies pre-elafin as a biomarker in ARDS. Am J Respir Cell Mol Biol. 2008;38(6):724-32. doi: 10.1165/rcmb.2007-0354OC.
180. Tejera P, O'Mahony DS, Owen CA, et al. Functional characterization of polymorphisms in the peptidase inhibitor 3 (elafin) gene and validation of their contribution to risk of acute respiratory distress syndrome. Am J Respir Cell Mol Biol. 2014;51(2):262-72. doi: 10.1165/rcmb.2013-0238OC.
181. Moreau T, Baranger K, Dadé S, et al. Multifaceted roles of human elafin and secretory leukocyte proteinase inhibitor (SLPI), two serine protease inhibitors of the chelonianin family. Biochimie. 2008;90(2):284-95. doi: 10.1016/j.biochi.2007.09.007.
182. Babaei S, Bayat M. Pentoxifylline accelerates wound healing process by modulating gene expression of MMP-1, MMP-3, and TIMP-1 in normoglycemic rats. J Invest Surg. 2015;28(4):196-201. doi: 10.3109/08941939.2014.1002642.
183. Nicaise AM, Johnson KM, Willis CM, et al. TIMP-1 promotes oligodendrocyte differentiation through receptor-mediated signaling. Mol Neurobiol. 2019;56(5):3380-3392. doi: 10.1007/s12035-018-1310-7.
184. Power G, Moore Z, O'Connor T. Measurement of pH, exudate composition and temperature in wound healing: a systematic review. J Wound Care. 2017;26(7):381-397. doi: 10.12968/jowc.2017.26.7.381.
185. Liu C, Lu X, Mao Z, et al. The diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for acute kidney injury in adults: a PRISMA-compliant meta-analysis. Medicine (Baltimore). 2017;96(27):e7484. doi: 10.1097/MD.0000000000007484.
186. Gibb SL, Zhao Y, Potter D, et al. TIMP3 attenuates the loss of neural stem cells, mature neurons and neurocognitive dysfunction in traumatic brain injury. Stem Cells. 2015;33(12):3530-44. doi: 10.1002/stem.2189.
187. Hendrickson CM, Gibb SL, Miyazawa BY, et al. Elevated plasma levels of TIMP-3 are associated with a higher risk of acute respiratory distress syndrome and death following severe isolated traumatic brain injury. Trauma Surg Acute Care Open. 2018;3(1):e000171. doi: 10.1136/tsaco-2018-000171.
188. Radomski A, Jurasz P, Sanders EJ, et al. Identification, regulation and role of tissue inhibitor of metalloproteinases-4 (TIMP-4) in human platelets. Br J Pharmacol. 2002;137(8):1330-8. doi: 10.1038/sj.bjp.0704936.