



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 additional 74 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, thereby 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 injuries (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 hydrolyse 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 randomly selected. Eleven rats were selected as the blank group. Forty-four rat KOA models were established, and the remaining 5 rats

were used for stem cell extraction. The rats were randomly divided into two groups, and the transplantation group was treated with ADMSCs transplantation. The KOA group was intragastrically administered with saline. The expressions of MMP-13 mRNA and DDR2 in rats were detected by RT-qPCR and immunohistochemistry. Correlation analysis was performed in MMP-13 mRNA and DDR2 expression levels in the KOA rats. After treatment, the indexes of Lequesne MG knee joints, MMP-13 mRNA and DDR2 in the transplanted rats were significantly lower than those in the KOA group ($P < 0.05$ 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 α Ib β 3 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 phys-

iological 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 angiotatin [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 angiotatin 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-1 β (IL-1 β) 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 vigdalipin [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- κ B 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- κ B, 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- κ B 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 located 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 anti-proteases 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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