Resistance of Bacteria to the Factors of the Innate Immune System, Mediated by Bacterial Proteases

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Introduction

Currently, database (www.ebi.ac.uk/merops/), contains data more than $9 \times 10^5$ peptidase. The MEROPS database uses a hierarchical, structure-based classification of the peptidases. Each peptidase is assigned to a family on the basis of statistically significant similarities in amino acid sequence, and families that are thought to be homologous are grouped together in a clan. There is a summary page for each family and clan. Incises only 3614 (0.4%) peptidases from them contains identifiers and in these 3614, only 372 (0.04%) are haws of both identifiers and EC number. Each peptidase is given a unique identifier known as a MEROPS ID. The MEROPS (ID) identifier consists of letters and numbers that reflects: the family identifier (three characters), a dot, and a three-digit number, e.g. S01.001. Peptidases from different organisms are assigned to a single ID when the available data indicates that they belong to the same catalytic type. Special forms of MEROPS ID are used for uncharacterized peptidases from model organisms, unassigned peptidases, non-peptidase homologues, pseudogenes and unsequenced peptidases.

All peptidases (proteolytic enzymes) are classified into MEROPS as nine catalytic types: aspartic peptidases, cysteine peptidases, Glu-peptidases, metallo-peptidases, asparagine-peptidases, serine-peptidases, threonine peptidases, unclassifiable peptidases and unknown peptidases.

The most numerous catalytic group of these enzymes is the serine peptidase (family S). Currently, it includes almost 334,140 peptidases, of various organisms. Then follow cysteine peptidases (about 176844 enzymes) and metallo-peptidases (about 296030 enzymes). Each catalytic type forms a family of peptidases, homologous and highly orthologous proteins similar structure of these catalytic centers.

In this review, proteolytic enzymes from microorganisms are considered. Many of them are pathogenic or opportunistic pathogens for humans. All these enzymes belong to the following catalytic types or families: family A (aspartic peptidases, clan AA, AE, AC, AF, AD), family C (cysteine peptidases, clan CA, CD, CM, CF, CO, CP, CQ), as well as the family M (metallo-peptidases, clan MA, ME, MC, MD, MG, MM) and family S (serine-peptidases, clan PA, PB, SE, PC, SF, SI).

Components of the Innate Immune System as Targets of Microbial Peptides

The Innate immunity is conceptually defined as the body's ability to neutralize the alien and potentially dangerous biomaterial (microorganisms, transplants, toxins, tumor cells and virus-infected cells). This system induces the cellular part (phagocyte system and less specialized cells) and the humoral innate immunity (represented by the main bactericidal components contained in the body fluids providing the so-called "chemical protection" from microorganisms, as well as the system of contact activation of blood coagulation, the complement system and fibrinolysis). An important component of innate immunity is the normal microflora protecting agains pathogenic microflora [1,2].

According to modern data, the magnitude of this component is very significant. In the biotopes of the skin and mucous membranes, there are about $10^{14}$ microorganisms belonging to commensals (normal microflora), their number, as a rule, exceeds the number of human cells several times [3].

Innate immunity active in skin is formed by the combined action of several systems. Firstly, it is a layer of keratinized skin epithelium, providing a waterproof physical barrier that limits the access of microorganisms to the underlying tissues. This physical barrier is strengthened by the so-called components of a chemical defense system consisting of antimicrobial peptides (such as cathelicidins, β-defensin, dermicidin, psoriasin, etc.) [4]. One of the key roles in chemical skin protection is played by fatty acids secreted by the sebaceous glands. The activity of these components in the skin significantly depends on its integrity. Different types of mucous membranes are impermeable to bacteria. The secrets of skin glands contain a wide range of antimicrobial peptides (AMP) and proteins that inhibit adhesion and invasion of microorganisms [5].
In addition, the antimicrobial protection of mucous membranes is enhanced by a complex lymphoid tissue associated with the mucosa (MALT, Mucosa-associated lymphoid tissue), which is rich in immunocompetent cells that coordinate the functions of both the innate and acquired immune system. How does innate immunity react to microorganisms?

The destruction of the skin protection barrier, mucous and introduction of pathogenic microorganisms is recognized by innate immunity using PRRs (PRRs-pattern recognition receptors). These receptors have a high affinity for conserved microbial molecular fragments, characteristic for a wide range of microorganisms (peptidoglycan, lipopolysaccharide, lipoteichoic acids, lipoproteins, CpG DNA, flagellin, β-glucan, etc.) and other pathogen-associated molecular components (PAMPs-pathogen-associated molecular patterns) [6].

The PRRs are represented in the body in three forms: soluble forms (e.g., lipopolysaccharide binding protein, C-reactive protein, mannose-binding lectin, surfactant proteins A and D); cellular receptors and opsonizing molecules (Toll-like receptors or TLRs, CD14); cytoplasmic inactivating the defense mechanisms.

In addition, the body has in its arsenal a powerful complement system, activation of which is an essential part of the innate mechanisms of antimicrobial protection, realized by anaphylotoxins (C3a, C3b). Chemokines and anaphylotoxins attract neutrophils from the bloodstream and activate their bactericidal activity. All these processes initiate acute inflammation, which is absolutely necessary for the effective elimination of microorganisms. It should be noted that monocytes/macrophages, neutrophils, NK cells constitute effector cells of innate immunity. Neutrophils after the killing of microorganisms undergo apoptotic death. Macrophages are able to survive a longer period and participate in resolving the inflammatory reaction. In addition to the classical components of innate immune response in human, a system of contact activation of blood coagulation plays a significant role in the formation of resistance to microbial infection [7,8]. It is generally recognized that the system of contact activation of blood coagulation is one of the recognizing subsystems of innate immunity [9]. The so-called receptors activated by proteases (PARs-protease-activated receptors) represent another direct link between the system of contact activation of blood coagulation and innate immunity. Typically, these receptors are expressed on epithelial, endothelial cells, as well as on leukocytes and platelets. They are activated by proteases of the blood coagulation system, which are mediators of the innate immune response. The PARs regulate various functions of leukocytes, participate in the activation of pro-inflammatory intracellular signaling systems. Thus, PARs are considered as an integral part of the antimicrobial signaling defense system of the organism [10,11]. Similar functions have been found for epithelial integrin receptors [12]. Despite the formed of innate immune response, some bacteria acquired and developed the ways of inactivating the defense mechanisms.

Bacteria have a whole spectrum of virulent properties that include and allow them to survive when interacting with the immune system of innate immune complex mechanism of proteolytic activity. The main goal of pathogenic bacteria proteolytic enzymes is the signal and effector molecules of immune defense. We identified the main strategic directions developed by the bacteria to suppress the most ancient system of body protection, namely is innate immunity:

1) Effects on the complement system and fibrinolysis processes
2) Disruption of the activation of the coagulation contact system blood
3) The interaction between cytokines and their receptors
4) Inactivation of antimicrobial peptides (AMP), chemokines and cytokines
5) Action on recognition receptors (receptors activated by proteases, PRRs-receptors)
6) Exposure to phagocytes and suppression of phagocytic reactions
7) Development of proteolytic systems of capture and assimilation of the heme and free iron of the organism
8) Influence on intracellular signaling pathways of immunocompetent cells.

Effects on the Complement System and Fibrinolysis

The complement system is an integral and vital part of the innate and acquired immune system. This system can be activated by three ways: the classic way of complement activation (antigen-antibody-dependent); lectin pathway molecules; an alternative way to activate complement (via binding of C3 to the surface of microorganisms). Pathogenic microorganisms have acquired the ability to destroy and bind components of complement to prevent their activation along appropriate paths.

The main targets of most bacterial proteases are C3 and C5 convertase complexes, in particular C3-protein and its activated forms, which are integral components of the C5-convertase complex. The cysteine protease (streptopain, SpeB, EC 3.4.22.10) of Streptococcus pyogenes cleaves the C3-component, preventing the formation of the C5-convertase complex, membrane-attack complex (MAC) and proinflammatory mediator-C5a [13]. The final effect leads to inhibition of both opsonization of bacteria and phagocytosis by neutrophils. Bacterial Streptopain also cleaves the properdin, forming the C5-convertase complex after the alternative complement activation [14]. It was found that the majority of Streptococcus sp. Produces C5a-peptidases from the family of the subtilisin serine proteases S.08.20 that cleave C5a in its N-terminal region and inhibit phagocytic clearance of microorganisms [15]. The protease PgtE (protein E, outer membrane protease E, EC 3.4.23.-, family A26.004) from Salmonella enterica cleaves several components of the complement system C3b, C4b and C5, affecting the activation of the convertase complex, which protect is bacteria from the action of complement [16]. Cysteine proteinase, StcE (family M 66.001), isolated from Escherichia coli O157: H7, cleaves the serpin C1 esterase inhibitor (C1-INH), a major regulator of the classical complement cascade [17,18]. These data suggest that by recruiting C1-INH to cell surfaces, StcE may protect both Escherichia coli O157:H7 and the host cells to which the bacterium adheres from complement-mediated lysis and potentially damaging inflammatory events [19].

Effects on the Processes of Fibrinolysis

Inflammatory response to bacterial infection leads to local thrombosis and blockade of the microcirculation system, which is an important mechanism to limit bacterial infection spread in tissues.
Bacterial to escape this response on plasmin (plasminogen) affect as, the most potent endogenous protease present in the serum. Thus, by affecting the fibrinolysis system, many pathogenic bacteria are easily disseminated and avoid elimination [20]. The spirochete Borrelia burgdorferi, responsible for the development of Lyme disease, change the system of plasmin activators [21].

Various bacterial species, including Streptococcus sp., and Staphylococcus sp. expresses specific plasminogen activators [22]. In contrast, streptokinase and staphylocinase, use plasminogen non-proteolytic activators. Some types of bacterial plasminogen activators are effective working in a similar way and causing effects as activators tPA, uPA host organism. Some gram-negative bacteria, including Yersinia sp., Shigella sp. (SopA), Salmonella sp. (OmpE, PgtE), Vibrio fisheri, Legionella pneumophila, Escherichia coli (OmpT), Enterobacter sp., Mesorhizobium sp., Erwinia sp., and Agrobacter tumefaciens express plasminogen activators that belong to the family A23-A26. The Omptin proteins (family A26.001) and represent aspartyl dependent protease, integrated into the outer membrane of bacterial cells [23]. Peptidase Pla (family A26) as one of the representatives of proteins of this family, from Yersinia pestis, is able not only to activate plasminogen, but also to inactivate α2-antiplasmin, an important plasmin inhibitor. A number of studies have shown the essential role of this enzyme for lymphogenous and hematogenous dissemination of Yersinia pestis [24].

Inhibition of Contact Activation of Coagulation by Bacterial Proteases

Activation of the blood coagulation system from contact with the bacterial cell surface leads to the generation of bactericidal peptides (kininogens, bradykinins), and stimulates the migration of inflammatory receptors. It is not surprising that cytokines and their receptors are the main molecular targets of a whole spectrum of bacterial proteases. Activation of PAR-2 leads to the formation of a protease-activated receptor (PAR) complex, which are activated by endogenous serine proteases. These receptors, activated by endogenous serine proteases, are present on platelets, endothelium, myocytes, T-lymphocytes and neurons. In humans, there are four types of receptors belonging to this family, PAR-1, 3, and 4 are activated by thrombin in physiological conditions, whereas PAR-2 can be activated by other proteolytic enzymes. Activation of PAR-2 leads to the formation of a pro-inflammatory response. Arginine-specific protease gingipain from Porphyromonas gingivalis is able to activate PAR-2 in neutrophils, pathogenic bacterial species form proteases that cleave and inactivate AMP. Human cathelicidin LL-37 is a direct target for digestion by the enzyme streptopain (family C10, EC 3.4.22.10) of Strepnotococcus pyogenes, elastase B (family M04.005) of Pseudomonas aeruginosa, gelatinase (cocolysin, family M04.007) of Enterococcus faecalis and metalloprotease (ZapA, family M 10.057, clan MA) of Proteus mirabilis [32]. Inactivation of LL-37 with bacterial proteases underlies the pathogenesis of the development of chronic ulcerative skin and mucosal defects, etiologically associated with infection of Pseudomonas aeruginosa, Enterococcus faecalis and Proteus mirabilis [33]. It should be noted that the ZapA metalloprotease of Proteus mirabilis is a necessary virulence factor of uropathogenic strains isolated from patients with a urinary tract infection [34]. This protease inactivates LL-37, and β-defensin (hBD1), that contribute to the antibacterial protection the urinary system. Decreased activity of hBD1 is one of the factors that facilitate the colonization Proteus sp. [35]. A similar scenario exists in Porphyromonas gingivalis, the main etiological agent of human periodontitis, with respect to the bactericidal activity of AMP from saliva and parodontal tissues. Gingipaines from these bacteria split several different AMP including LL-37, dermaseptin, histatin 5, cecropin, brevinin, α-defensin (HNP-1), hBD-1, hBD-2, hBD3 [36]. Local deficiency of LL-37 due to their proteolytic degradation, creates favorable conditions for the development of severe forms of periodontitis [37]. Catelicidin provides an innate immune defense of the skin against bacterial infections caused by gram-positive cocci (Staphylococcus aureus, Streptococcus pyogenes) [38]. Proteases of these species are capable of cleavage catelicidins thus aureolysin (family M4.009) Staphylococcus aureus ensures the inactivation of LL-37 in tissues infected with Staphylococcus sp. [39]. In addition, Staphylococcus aureus forms cysteine proteinases (staphopaines) that effectively inactivate tissue cystatins, which leads to an increase in the activity of tissue cathepsins in the inflammatory focus and rapid inactivation of AMP [40]. The gram-negative bacteria have a special system of enzymes of the family A26 peptidase (OmpTin, Protease 7, EC 3.4.23.49, family A26.001), localized in the outer membrane, which are also able to effectively inactivate AMP [41]. Serine proteinases, omptin, PgtE which is isolated from Salmonella enterica, cleaves α-helical cationic AMP, including LL-34, but does not inactivate protegrin or HNP-1 [42]. These data indicate that different omptin enzymes have certain specificity for AMP. The PgtE expression is regulated by the Fop/PhoQ sensitive microbial cell system that reacts to sublethal concentrations of cationic AMPs and through the degradation of these peptides, the Gram-negative bacteria proteases contribute to the survival of these bacteria in the human body [43].

Activation and Inactivation of Various Cellular Receptors by Bacterial Proteases

Receptors that are activated by proteases (PARs), refer to the subfamily of dual G-protein receptors, composed of seven transmembrane domains, which are activated by endogenous proteases [44]. Receptors, activated by proteases, under physiological conditions are normally activated by endogenous serine proteases. These receptors are expressed on platelets, endothelium, myocytes, T-lymphocytes and neurons. In humans, there are four types of receptors belonging to this family, PAR-1, 3, and 4 are activated by thrombin in physiological conditions, whereas PAR-2 can be activated by other proteolytic enzymes. Activation of PAR-2 leads to the formation of a pro-inflammatory response. Arginine-specific protease gingipain from Porphyromonas gingivalis is able to activate PAR-2 in neutrophils,
epithelial cells, resulting in the production of IL-6 in the site of infection [45-46]. The ability of this enzyme to activate PAR-1, 4 on platelets is also shown, leading to aggregation and microthrombosis in the infection site [47]. Number of have shown studies, that mice, deficient in the expression of PAR-2 receptors, were not affected by the development of periodontitis. Thus, a significant role of this type of receptors in the pathogenesis of the inflammatory reaction of the paradont in humans has been established [48].

Protease LepA (family S26.UNW), from by Streptococcus pyogenes activates NF-κB signaling pathway, through the activation of PAR-1, 2, 4-receptors and metallo-protease. Metalloprotease LasB (family M04.005) of Pseudomonas aeruginosa can destroy the extracellular domains of PAR-2 receptor and inactivate it [49]. The serralysin (family M10.051) of Serratia marcescens was able to activate PAR-2 receptor in carcinoma of the airways and HeLa cells lines, with subsequent activation of pro-inflammatory signaling pathways experimental cells [50]. The same ability to activate this type of receptor on epithelial cells of the stomach is set to proteases from Helicobacter pylori, which resulted in the increased production of pro-inflammatory IL-8 in the centers of colonization of this bacterium.

Effects on Chemokines

Chemokines are a superfamily of cytokines-small proteins (8-25 kDa). One group of chemokines stimulates the migration of immune cells to the site of infection. Another group regulates the processes of growth, maintenance of homeostasis and controls the development and differentiation of body tissues. About 50 chemokines have been found. Chemokine receptors are transmembrane proteins or G-protein coupled receptors (serpine receptors, GPCR). Modulation of chemokine activity by partial proteolysis with matrix metalloproteases is one of the main mechanisms mediating the migration of phagocytes to the inflammatory focus [51]. Bacterial proteases, with specificity to chemokine IL-8 was first described in Porphyromonas gingivalis. These proteases are a group of gingipaines (RgpA, RgpB, Kgp, family C25.001-C25.003) that being soluble increase the activity of IL-8 in tissues, thereby contributing to the massive infiltration by neutrophils into the site infected paradont. The bacterial cell associated on the contrary inactivate IL-8 by splitting it in several places of the polypeptide chain [52]. The Elastase B from Pseudomonas aeruginosa effectively destroys human CCL5 (RANTES), MCP-1 from monocytes, ENA-78, thereby violating the chemotaxis of T-lymphocytes, eosinophils and basophils. The degradation of chemokines by Pseudomonas aeruginosa proteases makes a significant contribution to the metabolism of chemokines in the respiratory tract and thus contributes to the chronicization of the inflammatory process the lung [53]. SpyCEP peptidase (cell envelope protease, family A S08.027) of Streptococcus pyogenes, can cleave the C-terminal domain of mouse chemokines of the group CXC and MIP-2. The ability to cleave IL-8 by SpyCEP peptidase Streptococcus pyogenes is one of the mechanisms of inhibiting migration and suppressing the neutrophil phagocytosis of these bacteria [54]. In addition, the ability to cleave GCP-2 (granulocyte chemotactic protein 2) and oncogenic growth factor alpha (GRO-α) of the main chemokines present in the human tonsils has been demonstrated for SpyCEP peptidase. The cleavage of GCP-2 and GRO-α by the SpyCEP peptidase nullifies their ability to primarily activate neutrophils, adversely affecting the innate immune response [55]. All these data together suggest that the SpyCEP peptidase is a very effective "weapon" used by Streptococcus sp. to suppress the phagocytic link in the innate immunity system [56].

Bacterial Proteases Affect the Intracellular Signaling Pathways

Binding of pathogens to PRP-receptors leads to signal transmission to the cell and activation of several signaling intracellular systems. First of all, they are mitogen-activated protein kinase systems (MAPK, ERK, NK and p38) and the signal pathway of the nuclear transcription factor κB (NF-κB), which regulate the production of pro-inflammatory cytokines, and the responses of innate immunity, including mobilization of neutrophils, activation of macrophages and isolation of bacterial effector molecules. The signal transfer cascade is feedback-regulated by a covalent modification of some intracellular factors: either by phosphorylation or by binding to SUMO-proteins that perform functions of modulators of intracellular enzymes. Some bacteria have the acquired ability to destroy modulators of these signaling pathways, by introducing into the host cells specific bacterial proteases that activate cell isopeptidases. Ultimately, there is a disruption in the transmission of the intracellular signal, which leads to apoptotic cell death. It is this survival strategy that demonstrates the pathogenic strains of Yersinia sp. (Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica). Injection of enzymes into host cells in all pathogenic strains of Yersinia sp. is carried out by type III secretory system (T3SS), whose proteins are encoded by the plasmid genome. The T3SS system includes the YopJ (family C55.001), which has high homology with the cytotoxic protease (clan CE) [57,58]. Enzymes homologous to YopJ from Yersinia enterocolitica (YopP) are capable of disrupting the intracellular signaling pathways responsible for the cell-producing transmitters of interferon, NF-κB, and MAPK systems [59,60,61].

Recently, it has been found that YopJ (family C55.001) is capable of exhibiting acetyltransferase activity; it is suggested that Yop/J P acetylates the MMPK kinase (MMK6, MEK2) of host cells, which blocks their subsequent phosphorylation and activation [62,63]. Along with YopI-like enzymes, other species of Gram-negative pathogenic bacteria form proteins related to Ubl-specific proteases (ubiquitin-specific) of the C48 family; for example, Ssel, peptidase (family C79) isolated from Salmonella enterica, suppresses intracellular degradation of IkB and, thus, inhibits the activation of NFκB [64]. Similar ChaDub peptidases expressed in Chlamydia trachomatis and protease ElaD of Escherichia coli have similar activity [65,66]. It is significant that ChaDub peptidase 1, 2 (CT868, CT867 peptidase, family C48.032, C48.033) and ElaD (family C79.001) are expressed only in pathogenic bacterial species [67]. Also, enzymes that affect modulators of intracellular signaling systems include cysteine peptidase YopT (family C58.001) from Yersinia pestis and Pseudomonas syringae (AvrPphB peptidase, family C58.002). The YopT enzyme cleaves the intracellular factors RhoA, Rac, and Cdc42 of GTPase in the host cells, thereby disrupting the actin polymerization and eventually disrupting the cell cytoskeleton [68]. On the example of macrophages-this leads to a loss of ability to phagocytize bacteria. Similarly, the intracellular GTPase and serine/threonine kinases in plant cells have the bacterial enzyme AvrPphB peptidase (family C58.002, clan CA) isolated from Pseudomonas syringae [69,70]. In contrast to the enzymes described above, which are introduced directly through the membrane into the host cell, the toxin from Bacillus anthracis enters the cell only with endocytosis, after which it moves from the endosomes to the cytoplasm and its metalloproteinase component, related to the lethal toxin cleaves the MKK kinases, thereby effectively blocking the activation of a genes, dependent on the NF-κB factor [71].
Effects on Phagocytes

Bacterial proteases are able to accelerate the premature apoptotic death of phagocytes, or are capable of inactivating their bactericidal activity. The very specific mechanisms of these processes are the manipulation of a cascade of modulators involved in intracellular signaling metabolic pathways [72]. In addition, the ability of selective proteolysis of antibodies in the "hinge" region has been shown for streptopain (SpeB, erythrotxin B, family C10.001) [73]. Thus, in vivo SpeB contributes to the intracellular survival of Streptococcus pyogenes in macrophages, as well as aureolysin (SepP1 g.p. Staphylococcus aureus, family M04.009) for the survival of Staphylococcus aureus in phagocytes [74]. Another mechanism used by bacteria for modify phagocytes is the proteolytic modification of specific receptors on their surface. The ability of bacterial proteases to induce cleavage cytokine receptors, for example, C5aR, as well as CD14, CD31, CD44, syndecan-1R and the urokinase-like plasminogen activator receptor has been shown [75]. The Staphylococcus aureus the mechanism of selective cleavage of CD11b on phagocytes by staphopain B (SpeB, family C47.002), cysteine proteinase, that provides effective elimination phagocytes [76]. Similar mechanisms on CD31 receptor on neutrophils have protease (gingipain, RgpB, family C25.003) from Porphyromonas gingivalis [77,78].

Final Consideration

Thus, in the course of their evolution, the bacteria acquired a whole system of specialized enzymes proteases that effectively affect various components of the host innate immune system. The further study of these enzymes will allow us to develop etioprotective agents for treating bacterial infections, as well as specific prevention and therapeutic approaches. It should be noted that an example of such an approach was the creation of a whole group of HIV protease inhibitors that are successfully used in the treatment of HIV infection.

Conflicts of Interest

The authors declare no conflicts of interest.

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