Biochimie xxx (2015) 1–18

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Antimicrobial proteins and peptides in human lung diseases: A friend and foe partnership with host proteases

Fabien Lecaille*, Gilles Lalmanach, Pierre-Marie Andrault

INSERM, UMR 1100, Pathologies Respiratoires: Protéolyse et Aérosolthérapie, Centre d'Etude des Pathologies Respiratoires, Equipe 2: « Mécanismes Protéolytiques dans l'Inflammation », Université François Rabelais, F-37032 Tours cedex, France

ARTICLE INFO

Article history:
Received 13 July 2015
Accepted 31 August 2015
Available online xxx

Keywords:
Antimicrobial peptides and proteins
Proteases
Inhibitors
Lung
Chronic obstructive pulmonary disease
Cystic fibrosis
Asthma

ABSTRACT

Lung antimicrobial proteins and peptides (AMPs) are major sentinels of innate immunity by preventing microbial colonization and infection. Nevertheless bactericidal activity of AMPs against Gram-positive and Gram-negative bacteria is compromised in patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and asthma. Evidence is accumulating that expression of harmful human serine proteases, matrix metalloproteases and cysteine cathepsins is markedely increased in these chronic lung diseases. The local imbalance between proteases and protease inhibitors compromises lung tissue integrity and function, by not only degrading extracellular matrix components, but also non-matrix proteins. Despite the fact that AMPs are somewhat resistant to proteolytic degradation, some human proteases cleave them efficiently and impair their antimicrobial potency. By contrast, certain AMPs may be effective as antiproteases. Host proteases participate in concert with bacterial proteases in the degradation of key innate immunity peptides/proteins and thus may play immunomodulatory activities during chronic lung diseases. In this context, the present review highlights the current knowledge and recent discoveries on the ability of host enzymes to interact with AMPs, providing a better understanding of the role of human proteases in innate host defense.

Contents

Abbreviations: α1-AT, α1-antitrypsin; AMP, antimicrobial peptide and protein; ASL, airway surface liquid; BALF, broncho alveolar lavage fluid; BM, basement membrane; Cat, cathepsin; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; CLD, cathelin-like domain; COPD, chronic obstructive pulmonary disease; CRD, carbohydrate recognition domain; GAG, glycosaminoglycan; GOLD, global initiative for lung diseases; ECM, extracellular matrix; HBD, human beta-defensin; hCAP, human cathelicidin antimicrobial peptide; HMWK, high molecular weight kininogen; HNE, human neutrophil elastase; HNP, human neutrophil peptides; LMWK, low molecular weight kininogen; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MMP, matrix metalloprotease; NSP, neutrophil serine protease; SLPI, secretory leucocyte protease inhibitor; SP, surfactant protein; SPLUNC1, short palate lung and nasal epithelium clone 1; TLR, toll-like receptor; TIMP, tissue inhibitor of metalloproteases; TNF, tumor necrosis factor.

* Corresponding author. INSERM, UMR 1100, «Pathologies Pulmonaires: Protéolyse et Aérosolthérapie», CEPR, Université François Rabelais, Faculté de Médecine, 10 Boulevard Tonnellé, F-37032 Tours cedex, France.
E-mail address: fabien.lecaille@univ-tours.fr (F. Lecaille).

http://dx.doi.org/10.1016/j.biochi.2015.08.014

1. Introduction

During inhalation of the inspired air (8000–15,000 L daily), the upper respiratory tract is continually exposed to the outside environment that contains a myriad of microorganisms (10^4-10^6 bacteria per m^3) [1]. The integrity of the human respiratory tract relies on the multi-component host defense system that involves structural, physical and functional mechanisms (innate and adaptive immune systems) against colonization by pathogenic microorganisms [2]. In the normal lung, in concert to the mucociliary clearance of inhaled microbes and production of chemokines and cytokines, the release of a large variety of antimicrobial peptides and proteins (AMPs) (e.g. cathelicidins, defensins, lysozyme, secretory leukocyte protease inhibitor, lactoferrin, collectins, elafin, mucins) into the lumen of the airways, constitutes one of the first line of defense against pathogens. Because of their multiple roles in innate immunity (host defense, inflammation, tissue regeneration), AMPs are increasingly studied [3–8] Despite this formidable arsenal, failure of the host defenses may occur in pulmonary diseases including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma. Actually, several AMPs that are known to be resistant to proteolysis are degraded and inactivated not only by bacterial proteases [9] but also by host proteases. Host proteases fulfill basic homeostatic tasks and participate positively to the processing of numerous components as well as in the repair and turnover of the extracellular matrix and basement membrane in lungs (for review: [10–12]). However, an imbalance of proteases-antiproteases network in favor to proteolysis is observed under pathophysiological conditions, which contributes to tissue injury and can dampen the antimicrobial activity of AMPs. First, we will give an overview on the most abundant airway AMPs (LL-37/hCAP-18, β-defensins, lactoferrin, lysozyme, SLPI, elafin, surfactant proteins SP-A and SP-D) and their regulation in human lung diseases including CF, COPD and asthma. Then, after a brief outline of pulmonary human proteases (with an emphasis on cysteine cathepsins) and their endogenous inhibitors, we will focus on the ability of these host enzymes to interact with AMPs. The aim of this review is to provide updated informations that may help to better understand the role of human proteases in innate host defense.

2. AMPs in the airway

Antimicrobial peptides and proteins (AMPs) constitute the most ancient and major weapon of host innate immune defense against different pathogenic microorganisms, including Gram-positive and -negative bacteria, viruses, fungi, parasites and tumor cells [13]. AMPs families consist of a diverse collection of peptides and proteins (~2500 AMPs have been reported up to now) that have been described in plants, insects, invertebrates and vertebrates (for review: [7,13–17]).

Major components of the airway surface liquid (ASL) with antimicrobial activity are peptides such as β-defensins, LL-37/CAP-18 or larger molecules, including lysozyme, lactoferrin, secretory phopospholipase A2, elafin, secretory leukocyte protease inhibitor (SLPI) and the surfactant proteins A and D [18]. Other substances such as mucins and the chemokine ligand CCL20 (also known as LARC and MIP-3α) contribute to the host defense [19,20]. AMPs act generally against microorganisms by disrupting the membrane integrity of pathogens, via different processes as detailed elsewhere [14,21].

2.1. Structure, expression and antimicrobial activity

Due to their large diversity, it is difficult to classify AMPs according to their origin or their mode of action. Nevertheless, AMPs share some common features. Most AMPs are amphipathic molecules with spatially separated clusters of hydrophobic and hydrophilic amino acids. In mammals, AMPs act against various microbes such as Gram-negative and Gram-positive bacteria, protozoa, fungi and some viruses. AMPs are involved in the aggregation, trapping and killing of pathogens and also play key immunomodulatory roles. AMPs have multiple ways to protect the host against these microorganisms, one of which relies on the cationic nature and the secondary structure of the peptides [22]. Nascent AMPs are synthesized as a pre-propeptide that possesses a N-terminal signal sequence for translocation to the endoplasmic reticulum, a

Please cite this article in press as: F. Lecaille, et al., Antimicrobial proteins and peptides in human lung diseases: A friend and foe partnership with host proteases, Biochimie (2015), http://dx.doi.org/10.1016/j.biochi.2015.08.014