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Cystatins

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Abstract

The cystatins comprise a superfamily of proteins related primarily by virtue of DNA and amino acid sequence homology. The superfamily consists so far of four distinct types of molecules ranging from the simpler low-molecular-weight type I and II cystatins, which function primarily to inhibit lysosomal cysteine proteinases (CPs), to the higher-molecular-weight type III and IV cystatins, which possess additional latent functions expressed only during episodes of injury and inflammation, or have evolved entirely novel inhibitory functions.

The role cystatins play in respiratory diseases such as asthma and COPD is poorly understood. However, they do modulate the immune response by acting directly on neutrophils, macrophages, and antigen presenting cells. It is also clear that they do not function independently of other proteolytic pathways involved in remodeling of the lung. Limited proteolysis inactivates cystatins allowing lysosomal CP activity to directly contribute to lung tissue degradation and also liberates kinins which signal through G-protein-coupled receptors to cause both constriction and dilation of the bronchioles, pain via stimulation of sensory nerves, mucus secretion, cough, and edema.

Introduction

The human cystatins comprise a superfamily of potent protein-based inhibitors of cysteine proteinases (CPs). It is one of the many protein proteinase inhibitor superfamilies that are involved in regulating mammalian homeostasis, including the serpins (e.g., α_1-antitrypsin; AAT) and low-molecular-weight kunitz (e.g., tissue factor pathway inhibitor; TFPI), and kazal-type (e.g., pancreatic secretory trypsin inhibitory; PSTI) inhibitors. Current knowledge of their function suggests that they primarily serve to inhibit the activity of lysosomal proteinases that may be released during normal or pathological cellular or tissue remodeling events.

The first cystatin described was isolated from chicken egg white in 1963 and found to exhibit potent inhibitory properties against the CPs papain and ficin. The name 'cystatin' was proposed by Barrett *et al.* in 1963 and later used to describe homologous proteins in the same superfamily. The first full sequence of a human cystatin was that of cystatin C. There are more than a dozen human cystatins all with different properties, unique distribution patterns, and functions. These have been grouped into four main cystatin types on the basis of DNA and protein sequence homology and over the last few years the superfamily has expanded to include additional CP inhibitors, molecules that have no CP inhibitory activity, and yet others that have evolved functions unrelated to CP inhibition.

The Cystatin Superfamily

Type I Cystatins

Type I cystatins are intracellular and present in the cytosol of many different cell types. They are typically 100 amino acids long and lack disulfide bonds. There are two human cystatins called 'stefins' A and B to stress their difference from other cystatin superfamily members, but they do contain a general structure similar to the 'cystatin-fold' of other cystatins and similar CP inhibitory activity. In evolutionary terms, stefins A and B are closely related and form a distinct subgroup.

Type II Cystatins

Type II cystatins are typically 120–125 residues long and contain two disulfide bonds. They are translated with a secretory peptide leader sequence and are considered extracellular but can also be found intracellularly. They are broadly distributed and can be found in most body fluids. Mammalian type II cystatins all present two disulfide bridges at the C-terminal end of the sequence with 10–20 residues between the cysteines. Significant diversity in the type II superfamily members arises from the existence of multigene families encoding many different proteins (Table 1) and by polymorphisms affecting the coding sequence and function of the protein. Several diseases are associated with functional deficiencies or aggregation states of certain type II cystatins. The 'classical' type II cystatins C, D, S, SA, and SN are >50% identical at the protein sequence level. In addition, several posttranslational modifications are found in the members of this family. They may also be glycosylated or phosphorylated. Examples of these are cystatins E/M (glycosylated on N108) and cystatins S and SN (consensus phosphorylation sites at S2 and S98, respectively). Cystatin S has been isolated from nasal and bronchoalveolar (BAL) fluids with varying states of phosphorylation, but the significance of this is currently unknown.

Type III Cystatins

These are multidomain proteins first described as kinin precursor proteins or kininogens. There are two types of human kininogens: high- and low-molecular-weight kininogens. These proteins are of high-molecular mass (60–120 kDa) and present three tandemly repeated type-2 like cystatin domains (D1, D2, and D3) with a total of eight disulfide bridges (six conserved and two additional at the beginning of cystatin domains D2 and D3). The D2 and D3 domains possess CP inhibitory activity similar to the type II cystatins. They are glycosylated proteins but the glycosylation sites are not present in the cystatin domains. Kininogens are expressed intravascularly and are found in blood plasma. However, in addition to their function as CP inhibitors, the kininogens serve as substrates for a diverse group of serine proteinases collectively termed the kininogenases. The kininogenases liberate the kinin family of inflammatory peptides from the parent molecules. The kinins consist primarily of bradykinin (BK) and kallidin (lysyl bradykinin). BK is a nine amino acid peptide released during inflammation and tissue injury that possesses both direct and indirect actions in the airways including bronchoconstriction and bronchodilation, stimulation of cholinergic and sensory nerves, increased mucus secretion, and cough and edema resulting from promotion of microvascular leakage. Its activities are mediated primarily via the B_1 and B_2 G-protein-coupled receptors.

Type IV Cystatins

The type IV cystatins are a small family of abundant fetal and bone glycoproteins known as the fetuins. The two related human members of this family are α_2 Heremans Schmid glycoprotein (α_2-HS glycoprotein) and histidine-rich glycoprotein (HRG). The fetuins are N- and O-glycosylated and phoshorylated. The N-terminal region consists of two tandem type II cystatin domains followed by a C-terminal region comprised of a histidine-rich domain between two proline-rich domains. The N- and C-terminal regions are linked by a disulfide bond. α_2-HS has a structure similar to HRG except that it lacks the histidine-rich tandem repeat. Unlike the cystatin domains in the kininogens, the fetuins are devoid of CP inhibitor activity and consistent with this, they lack the conserved structural motifs responsible for CP inhibition. Surprisingly, orthologs have been found in snake venom that lack CP inhibitory activity but possess metalloproteinase inhibitory functions.

Structure: Function of Cystatins

The alignment of cystatin sequences has identified three functional regions that have been conserved for more than a billion years of evolution and are responsible for the CP inhibitory activity of the superfamily: a glycine (G) residue in the N-terminal region of the molecule, a glutamine (Q) – X – valine (V) – X – glycine (G) motif (QXVXG: the 'cystatin motif') in one hairpin loop (see later), and a proline (P) – tryptophan (W) motif in a second hairpin loop. These regions form a surface on the cystatin molecule that can dock and bind into the enzymatically active site(s) of papain-like CPs. The classic example of a type II cystatin is cystatin C, for which the X-ray crystallographic structure of the chicken protein has been solved (Figure 1). The main feature of the structure is a five-stranded β-sheet wrapped around a five turn α-helix commonly referred to as the 'cystatin fold'. The N-terminal 10 residues are disordered and flexible and the conserved G11 residue is present at the N-terminus of the five turn α-helix. The QXVXG motif is found on a hairpin loop located between β-strands B and C and the PW motif on a hairpin loop between β-strands D and E. Collectively, these three

Table 1 Cystatin genes, selected family members, and functions

Cystatin type	*Members*	*Common name(s)*	*Chromosomal Location/ (gene name)*	*Location*	*Function*	*Disease association*
I	A	Stefin A, (epidermal SH-protease inhibitor)	3cen q21	Intracellular, skin, blood	Cysteine proteinase inhibitor (CPI)	
	B	Stefin B, (CPI-B)	21	Intracellular, broad tissue distribution	CPI	Progressive myoclonus epilepsy
II	C	Post-γ-globulin	20p11.21 (*CST3*)	Widespread tissue/body fluids	CPI	Hereditary cystatin C amyloid angiopathy (HCCAA)
	D		20p11.21 (*CST5*)	Saliva, tears	CPI	
	E/M		11q13 (*CST6*)	Epidermal keratinocytes, sweat glands	CPI	Type 2 harlequin icthyosis
	F	Leukocystatin	20p11.21 (*CST7*)	Intra- and extra-cellular, hematopoietic cells		Inflammatory lung disorders
	S		20p11.21 (*CST4*)	Saliva, tears, urine		
	SN		20p11.21 (*CST1*)			
	SA		20p11.21 (*CST2*)			
III	L-kininogen	α_2-CPI	3q26-qter	Blood, body fluids	CPI, regulators of vascular permeability, bronchoconstriction	Inflammatory lung disorders
	H-kininogen	α_1-CPI				
IV	Fetuins	α_2-HS glycoprotein HRG	3q27	Fetal, bone		

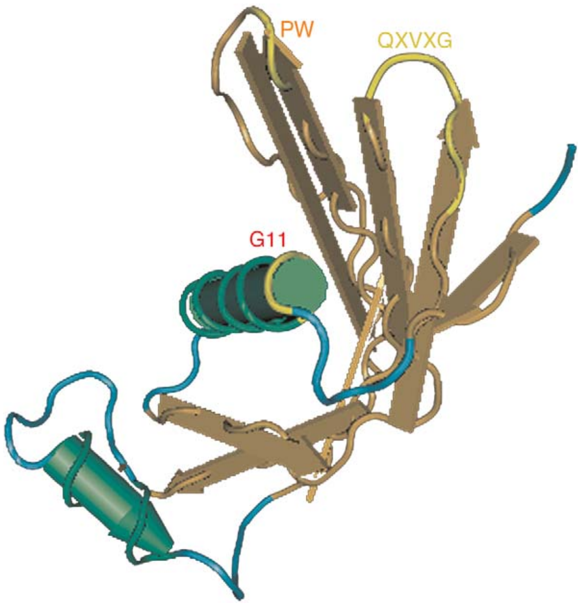

Figure 1 Three-dimensional structure of chicken cystatin C. A five-turn α-helix (green) is in the center of the structure. The conserved G11 residue is highlighted in yellow at the amino-teminal end of the α-helix. The conserved QXVXG motif is on a hairpin loop between β-sheet strands B and C. The conserved PW motif is on a hairpin loop between β-sheet strands D and E.

regions form a wedge-shaped edge complementary to the active site of the CP with many side-chain interactions. Each domain interacts with the target proteinase independently and binding of cystatins to CPs may or may not result in conformational changes in either protein. For example, cystatin binding to papain does not induce any conformational change in either protein whereas binding to cathepsin B involves the initial displacement of a loop occluding the active site to allow subsequent tight binding to occur. Cystatins differ considerably in their ability to displace the loop of cathepsin B.

In most cases, the affinity of the cystatins for their respective target CPs is very high with inhibitory constants (K_i's) in the nanomolar (nM) range but in several instances, where values may be in the micromolar (μM) range, effective inhibition may result from high local concentrations of the cystatins. Examples of this are the S-like cystatins which exist in high concentrations in saliva and tears.

Cystatins and Respiratory Health

Cystatins serve at least three functions in respiratory health and disease: they can directly inhibit endogenous or exogenous CPs; they can modulate the activity of the immune system against inhaled bacteria and viruses and their degradation products (kinins) are some of the most potent naturally occurring mammalian inflammatory agents. All the three functions are critical for the maintenance of respiratory health and, in the settings of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), all the three contribute to the acute and chronic nature of these diseases. However, with the exception of the proinflammatory functions of the type III cystatins (kininogens), the contribution of cystatin superfamily members to pulmonary health and disease is poorly understood.

Cystatins: Inhibitory Functions and Interaction with Other Proteolytic Systems

A well-established mechanism for the loss of lung function observed during the progression of emphysema is the enlargement of the pulmonary airspaces due to an imbalance in degradative proteases and their respective inhibitors (*see* **Chronic Obstructive Pulmonary Disease**: Emphysema, Alpha-1-Antitrypsin Deficiency; Emphysema, General). The CPs almost certainly contribute either directly or indirectly to this degradation, in particular, lysosomal cathepsins (cat) B, H, K, L, and S (*see* **Cysteine Proteases, Cathepsins**). Increased concentrations of cat L have been detected in the BAL fluids of patients with emphysema and alveolar macrophages from patients with COPD secrete more CP activity than macrophages from normal smokers or nonsmokers despite the fact that cystatin C concentrations are also increased. Direct inhibition of CP activity by the cystatins (primarily type II) in normal lung tissue likely contributes to the protection of the elastic lung tissue by directly inhibiting these CPs. The cystatins and CPs do not operate independently of other degradative systems (and their respective inhibitors) but participate in feedback systems that can produce profound changes in proteolytic activity referred to as the proteolytic burst (Figure 2). For example, several matrix metalloelastases, produced by inflammatory cells or activated airway epithelium, can inactivate AAT. Bronchial epithelial cells secrete procathepsin B and cystatin C, both of which are substrates for neutrophil elastase. Procathepsin B is activated by neutrophil elastase while human cystatin C is inactivated by cleavage between amino acids G11 and G12. The latter observation may explain why active cat L has been found in the BAL fluid of COPD patients despite the presence of elevated cystatin C levels. Cystatin C is also produced by monocytes and macrophages and its release is downregulated by proinflammatory lipopolysaccharide (LPS) and interferon gamma (IFN-γ), which coincidentally increase

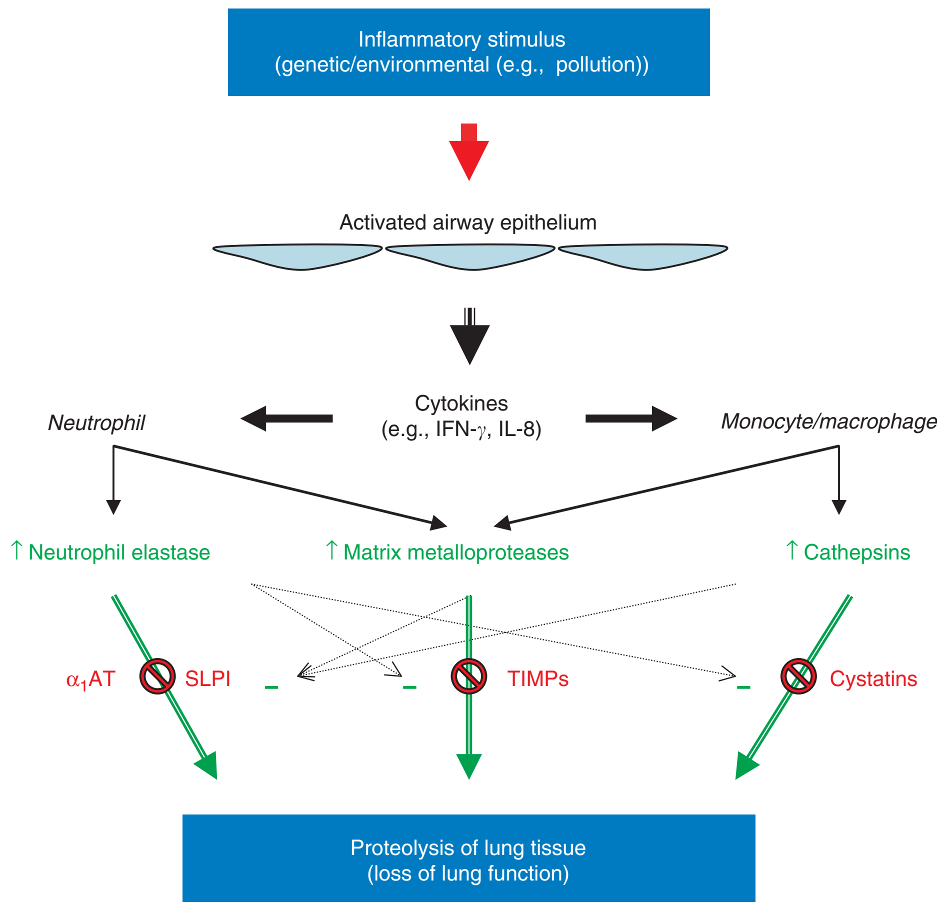

Figure 2 Interactions of inflammatory pathway proteases and inhibitors. IFN-γ, interferon gamma; IL-8, interleukin 8; α_1AT, alpha 1-antitrypsin; TIMPS, tissue inhibitors of metalloproteases; SLPI, secretory leukocyte protease inhibitor.

the expression of cat B, D, H, L, and S. In addition, cat B, L, and S can inactivate secretory leukocyte protease inhibitor (SLPI).

Endogenous cystatins are not able to inhibit elastolytic CPs produced by bacterial pathogens such as *Staphylococcus aureus* or *Clostridium histolyticum*, but other proteases, such as V8 protease produced by *S. aureus*, may contribute to an increased elastolytic burden in the lung by inactivating AAT directly.

In addition, some potent inhaled allergens possess cystatin inhibitory activity (e.g., cat Fel D3) or CP activity (e.g., dust mite Der P1) and these may have direct effects on lung epithelium and immune surveillance cells of the lung.

Immunomodulatory Functions of Cystatins

Cystatins have a wide range of effects in and on the immune cells present in the pulmonary space. Cystatin C is chemotactic for neutrophils, yet inhibits superoxide production and neutrophil-mediated phagocytosis. It also modulates macrophage responses to IFN-γ by increasing production of nitric oxide six- to eightfold via a mechanism independent of its CP inhibitory activity; however, it also increases the production of TNF-α and IL-10.

CPs have essential functions in antigen presenting cells (APCs) and cystatin C also plays an important role in modulating major histocompatibility complex (MHC) class II-mediated antigen presentation in peripheral dendritic cells by controlling cat S-mediated degradation of the invariant chain (Ii). This processing prevents targeting of the MHC class II molecules to the lysosomes for degradation. During maturation of APCs in the lymphoid tissue, endosomal cat S activity increases due to a decrease in the levels of cystatin C. Cathepsins K and F can also degrade Ii and cat K is found in bronchial epithelial cells that can serve as nonprofessional APCs. In contrast, cat F's expression is restricted to hematopoietic cells making it a prime candidate for a role in immunomodulation in these cells.

Finally, some members of the human cystatin superfamily (e.g., cystatin S) have potent bactericidal

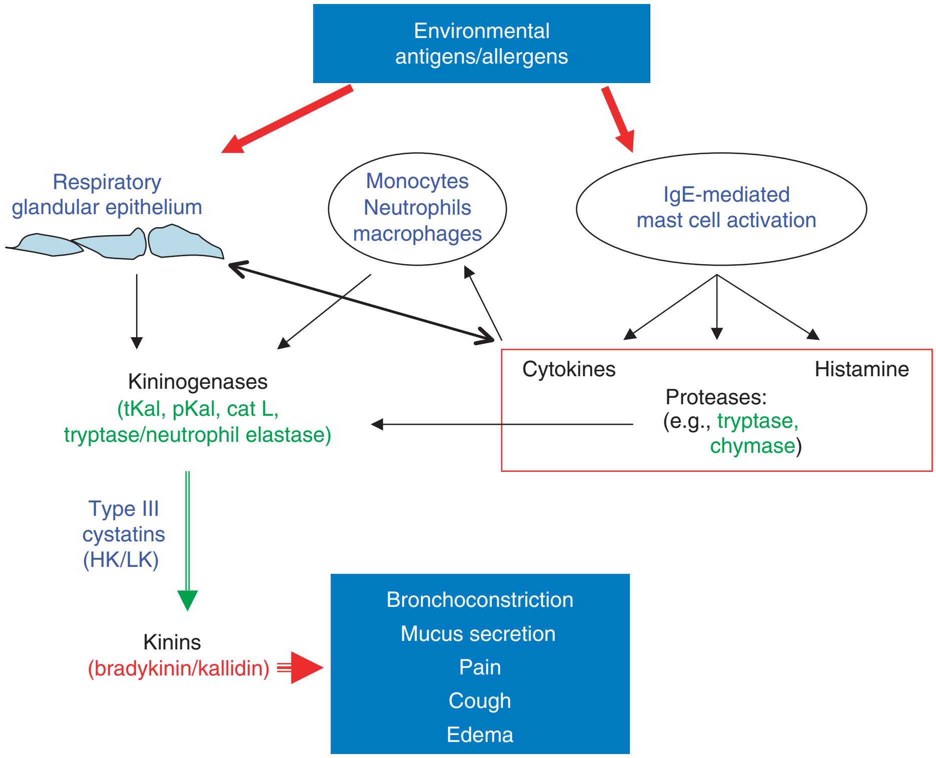

Figure 3 Generation of proinflammatory kinins from type III cystatins. tKal, tissue kallikrein; pKal, plasma kallikrein; cat L, cathepsin L; HK, high-molecular-weight kininogen; LK, low-molecular-weight kininogen.

activity unrelated to CP inhibitory activity which resides in specific peptide sequences present in the structure. Others (e.g.,C, D, and S) are able to block the replication of certain viruses. Cystatin C is a potent inhibitor of herpes simplex virus (HSV)-1, whereas cystatins C and D both inhibit coronavirus replication in human lung cells. The likely mechanism of action involves cellular uptake followed by inhibition of the host or viral CPs required for viral replication.

Generation and Function of Proinflammatory Kinins from Type III Cystatins

Perhaps the best understood role for cystatins in respiratory health comes from our current understanding of how BK and kallidin are released from precursor kininogens (type III cystatins) and the multiple direct and indirect effects they have on the respiratory system.

Under inflammatory conditions, there are multiple kininogenases that could contribute to kinin generation in the lung (Figure 3). Plasma kallikrein (pKal), tissue kallikrein (tKal), cat L, and a mixture of neutrophil elastase and mast cell tryptase are all able to liberate kinins from kininogens. In the case of high-molecular kininogen, degradation by pKal creates a kinin-free two-chain disulfide-linked molecule containing a heavy chain and a light chain that retains CP inhibitory activity.

tKal has been identified as the major kininogenase of the airway and cleaves both HK and low-mole cular-weight kininogen to yield lysyl-bradykinin (kallidin). In asthmatic airways, the underlying glandular epithelium releases tKal that contributes to the intial phase of kinin generation but the recruitment of activated monocytes, neutrophils, and alveolar macrophages contributes to the late increases in tKal that are associated with the development of airway hyper-responsiveness (AHR). Activated mast cells, macrophages, and neutrophils also release the tryptase, cat L, and elastase that contribute to kinin generation. It has been suggested that this mechanism also contributes to the etiology of other chronic inflammatory conditions such as chronic bronchitis. The generation of kinins by pKal may represent a more acute inflammatory response such as observed during acute pneumonia.

Kinins cause bronchoconstriction in asthmatic subjects when given by inhalation or intravenously. Their effects and mechanism of action are described in more detail in **Kinins and Neuropeptides:** Bradykinin.

Conclusions

The cystatins comprise a superfamily of proteins related primarily by virtue of DNA and amino acid sequence homology. The superfamily consists so far, of four distinct types of molecules ranging from the simpler low- molecular-weight type I and II cystatins, which function primarily to inhibit lysosomal CPs, to the higher-molecular-weight type III and IV cystatins, which possess additional latent functions expressed only during episodes of injury and inflammation, or have evolved entirely novel inhibitory functions.

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See also: **Chronic Obstructive Pulmonary Disease**: Emphysema, Alpha-1-Antitrypsin Deficiency; Emphysema, General. **Cysteine Proteases, Cathepsins**. **Kinins and Neuropeptides**: Bradykinin.

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Secretory Leukoprotease Inhibitor and Elafin

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Abstract

Secretory leukoprotease inhibitor (SLPI) and elafin are acid-stable, low-molecular-weight antiproteinases that are produced by the goblet cells, Clara cells, and alveolar type II cells in the pulmonary epithelium, and are also present in macrophages, while neutrophils contain SLPI. SLPI inhibits neutrophil elastase, cathepsin G, trypsin, chymotrypsin, and chymase. Elafin inhibits neutrophil elastase and proteinase-3. SLPI is 11.7 kDa; elafin (6 kDa) is a cleavage product of pre-elafin (also called trappin-2), which is 9.9 kDa. The inhibitory site of both inhibitors resides in the C-terminal four disulfide whey acidic protein (WAP) domain, which has 40% homology, and they belong to the WAP family of proteins located on chromosome 20q12–13. The N-terminal WAP domain of pre-elafin contains a transglutaminase substrate domain that enables the molecule to become tethered to cell surfaces and matrix proteins; proteolytic cleavage releases the C-terminal 6 kDa inhibitory domain. SLPI is also found in close association with elastic tissue, possibly reflecting its cationic properties. SLPI and elafin have antimicrobial activity against Gram-positive and Gram-negative bacteria, while SLPI has also been shown to have antiviral and antifungal properties. In addition, SLPI and elafin are immunomodulatory, interacting directly with lipopolysaccharide to subdue its inflammatory activity, and inhibiting release of mediators from inflammatory cells. SLPI also plays a significant role in wound healing, partly by preventing proteolytic activation of proinflammatory mediators. SLPI and elafin levels and activity change during lung diseases (e.g., chronic obstructive pulmonary disease, acute respiratory distress syndrome, and pneumonia), reflecting the degree of inflammation, proteolytic load, and oxidative stress. The possibility of SLPI and elafin therapy is under active investigation.