

Secretory leukoprotease inhibitor: partnering α_1 -proteinase inhibitor to combat pulmonary inflammation

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Abstract

Secretory leukoprotease inhibitor (SLPI) is a low molecular weight serine proteinase inhibitor, notably of neutrophil elastase (NE), which is synthesised and secreted by the pulmonary epithelium. SLPI plays an important role in limiting NE-induced pulmonary inflammation and, significantly, it also possesses anti-HIV activity. SLPI is a significant component of the anti-NE shield in the lung which has different reactivity from, and is therefore complementary to, the anti-NE action of α_1 -proteinase inhibitor (α_1 -PI). Inhaled recombinant SLPI (rSLPI) could prove beneficial in partnership with α_1 -PI in the treatment of a number of inflammatory lung disorders including emphysema, chronic bronchitis, cystic fibrosis, and adult respiratory distress syndrome.

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Inflammatory lung diseases commonly involve an influx of polymorphonuclear neutrophils (PMN) as part of the natural defence against inhaled organisms, foreign particles, and toxic agents. This influx is normally beneficial. Part of the defence mechanism involves release from the PMN of reactive oxygen species and proteolytic enzymes, the actions of which are tightly regulated by endogenous antioxidants and antiproteases, respectively. The significance of the latter control mechanism was clearly illustrated by the observation that the development of emphysema in certain patients was related to an hereditary deficiency of α_1 -proteinase inhibitor (α_1 -PI),¹ the major serum inhibitor of neutrophil elastase (NE). For some 20 years or so α_1 -PI was proposed as the sole inhibitor of NE in lower respiratory tract secretions. Nevertheless, this proposal was controversial. Many European researchers believed that there must have been at least one other NE inhibitor because the amount of NE inhibitory activity in bronchoalveolar lavage fluid (BALF) could not be accounted for by the levels of α_1 -PI present. Thus, considerable effort was devoted to identifying the uncharacterised inhibitor(s) in respiratory tract secretions. This proved a difficult task. However, it is now indisputable that other antiproteases, including

secretory leukoprotease inhibitor (SLPI, pronounced SLIPPY, also known as mucus proteinase inhibitor) and elafin, a smaller molecule related to SLPI, exist. The acronym for SLPI is appropriate as one reason for its elusiveness was that it readily slipped through the net! Despite having a molecular weight of 12 kD, SLPI can pass through concentrating membranes with a molecular weight cut off point of 5 kD.

Scientific basis

SLPI is an unglycosylated protein synthesised by airway and non-ciliated bronchiolar secretory epithelial cells. It can be secreted either apically into the airways or basally, directly into the interstitium. The level of SLPI in lung secretions varies considerably (10-50% of total NE inhibitors) throughout the respiratory tract, depending upon airway generation and disease state of the lung.² Sputum typically contains a higher percentage of SLPI than lower respiratory tract secretions. SLPI is a hydrophobic cationic protein and, thus, will bind readily to NE and some of its substrates - for example, elastin/extracellular matrix. Unlike α_1 -PI, it can inhibit elastin-bound NE. In addition, the interaction between SLPI and NE is reversible, facilitating transfer of NE to α_1 -PI. Inactive NE: α_1 -PI complexes are cleared via the lymphatic vessels and blood while SLPI is probably "recycled" to mop up remaining uninhibited NE.³

NE is pro-inflammatory (fig 1) and SLPI therefore has an important anti-inflammatory role. Interestingly, in vitro NE upregulates epithelial cell SLPI mRNA,⁴ suggesting feedback control. Similar mechanisms may occur in vivo. Other inflammatory mediators, including interleukin 1 β and tumour necrosis factor, have a similar stimulatory effect on SLPI mRNA production in lung epithelial cell lines.⁵ Local induction of SLPI synthesis is crucial as, via inhibition of NE, it not only suppresses the action of NE but also breaks the cycle of inflammation - for example, NE-induced production of IL-8 (PMN chemoattractant) by pulmonary epithelium (fig 1).⁶ In addition, inhalation of recombinant SLPI results in increased glutathione levels in human lung secretions.⁷ An increase in lung antioxidant capacity is likely to protect α_1 -PI from oxidative inactivation at the reactive site methionine residue.

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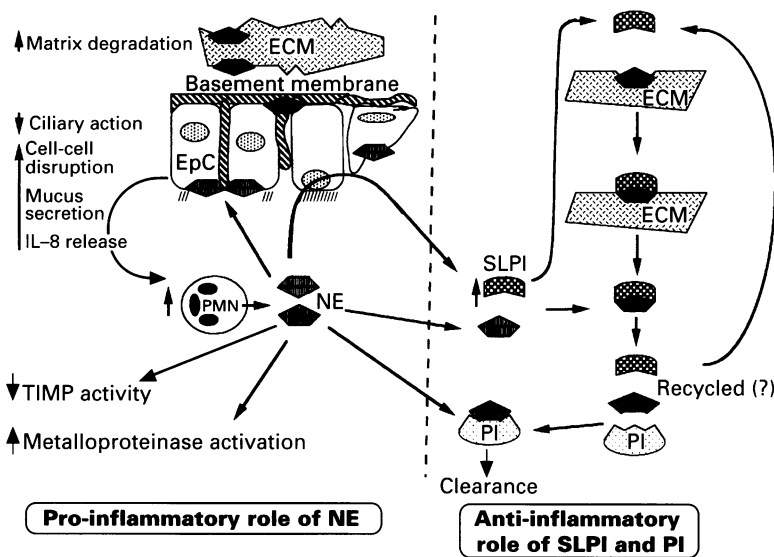


Figure 1 Diagrammatic representation of the possible anti-inflammatory role of secretory leukoprotease inhibitor (SLPI) in the lung. Polymorphonuclear neutrophil (PMN) influx leads to release of neutrophil elastase (NE) which has a number of pro-inflammatory effects. These include activation of metalloproteinases and inactivation of their inhibitors, tissue inhibitors of metalloproteinases (TIMP), which enhances the proteolytic potential. There is increased extracellular matrix (ECM) degradation. NE also affects epithelial cells (EpC), causing cell-cell disruption, increased mucus secretion, and decreased ciliary activity. These effects are perpetuated by the increased EpC release of chemokines such as interleukin 8 (IL-8), a chemoattractant for PMN. Basal release of SLPI from epithelial cells may be one mechanism by which the lung controls the extent of NE action; SLPI inhibits free and ECM-bound NE, enabling clearance from the lung via subsequent irreversible inhibition of NE by α_1 -proteinase inhibitor (PI). There may also be upregulation of SLPI transcription by NE to stimulate further release of SLPI.

Therapeutic potential

One of the anti-inflammatory mechanisms of glucocorticosteroids, especially fluticasone, may be to stimulate SLPI mRNA levels in airway epithelial cells,⁸ although there is no evidence to date for translation of the SLPI mRNA. However, since rSLPI is identical to the native unglycosylated protein, it is ideally suited to use therapeutically to supplement endogenous SLPI levels. For example, in normal subjects aerosolised rSLPI has a pulmonary retention time of more than 24 hours.⁹ Furthermore, studies in sheep lungs show that aerosolised protein is not altered in any way during administration and, importantly, the anti-NE capacity of BALF increases fourfold.¹⁰ Two important groups of patients in which NE is thought to cause tissue damage are those with cystic fibrosis and those with emphysema associated with α_1 -PI deficiency. One of the problems of using aerosolised rSLPI has been inefficient delivery to affected or poorly ventilated areas of the lung¹¹ which suggests that the most beneficial treatment might be prophylactic. Nevertheless, rSLPI has been successfully administered to patients with cystic fibrosis who showed a marked reduction in the NE activity of the BALF.⁹ Furthermore, it may be particularly useful alongside DNase I treatment since release of digested DNA causes a shift in the equilibrium favouring dissociation of the SLPI:NE complex, thus potentiating proteolytic activity in sputum. Exogenous rSLPI would counteract this. It is feasible that rSLPI could be used to treat other inflammatory lung disorders which involve NE

including emphysema, bronchiectasis, pulmonary fibrosis, acute lung injury and bronchopulmonary dysplasia. Probably the most effective treatment would entail combining SLPI and α_1 -PI, particularly since oxidised SLPI, unlike oxidised α_1 -PI, remains a potent protease inhibitor, especially at high concentrations, and despite containing methionine at its NE inhibitory site.¹²

Conclusion

SLPI, and possibly its relative elafin, works in partnership with α_1 -PI to control the destructive and pro-inflammatory activity of NE. Although rSLPI is available for therapeutic purposes, clinical trials are still in their infancy. We now know that SLPI is an ubiquitous molecule present in the gastrointestinal tract, skin, seminal fluid, and cervical mucus as well as in respiratory tract secretions. Perhaps the most exciting recent discovery is that SLPI is the only protein present in saliva that possesses anti-HIV activity at physiological concentrations.¹³ It can also protect human T cells from HIV infection. This may have important implications in protection of the lung from virally related diseases, particularly in the face of a compromised SLPI screen. In the latter respect it is worth noting that low BALF levels of SLPI have been documented in apparently healthy subjects. It is not known whether such subjects are relatively more susceptible to NE-mediated lung injury.

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