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MINIREVIEW

Anti-Inflammatory and Antimicrobial Roles of Secretory Leukocyte Protease Inhibitor

Stergios Doumas,[1] Alexandros Kolokotronis,[2]* and Panagiotis Stefanopoulos[3]

Private Practice, Manchester, United Kingdom,[1] and Dental School, Aristotle University of Thessaloniki, Thessaloniki,[2] and Hellenic Army, Athens,[3] Greece

Human secretory leukocyte protease inhibitor (SLPI) is an 11.7-kDa cationic protein and a member of the innate immunity-associated proteins. It is a nonglycosylated, highly basic, acid-stable, cysteine-rich, 107-amino acid, single-chain polypeptide (50). The SLPI gene, along with the elafin gene, is a member of the trappin gene family. The products of this family are characterized by an N-terminal transglutaminase domain substrate and a C-terminal four-disulfide core (37). These two domains (COOH terminal and NH_2 terminal) share about 35% homology (56). Each of these domains has distinct enzyme activities.

The tertiary structure of the SPLI molecule resembles a boomerang, with each arm carrying one domain (14). The four-in-each-domain disulfide bridges formed between the cysteine residues, as well as the two-domain interaction, contribute to the conformation and efficacy of the molecule (17, 26, 38).

The human SLPI gene is localized on chromosome 20q12-13.2 (21). The SLPI gene consists of four exons and three introns and spans approximately 2.6 kb (21, 48). To date, no polymorphism of the SLPI gene and no state of SLPI deficiency have been found (56).

Historically, SLPI was first isolated from secretions of patients with chronic obstructive pulmonary disease and cystic fibrosis and was thereby considered a major antielastase inhibitor (18, 33, 49). SLPI is produced by neutrophils, macrophages, beta-cells of pancreatic islets, epithelial cells investing the renal tubules, acinar cells of parotid and submandibular glands, acinar cells of submucosal glands, and epithelial cells lining mucous membranes of respiratory and alimentary tracts (1, 8, 9, 20, 30, 34, 40). SLPI was originally isolated from parotid saliva (50) and has been detected in a variety secretions such as whole saliva, seminal fluid, cervical mucus, synovial fluid, breast milk, tears, and cerebral spinal fluid, as in secretions from the nose and bronchi, etc. (9, 10, 26, 35, 40). The SLPI gene was found to be expressed in lung, breast, oropharyngeal, bladder, endometrial, ovarian, and colorectal carcinomas, and SLPI detection is correlated with poor prognosis (11, 59). SLPI is also found in neurons and astrocytes in the ischemic brain tissue (58). Finally, SLPI was found to play a pivotal role in apoptosis and wound healing (2, 31, 47). Given that SLPI is a ubiquitous protein, it has received many alternative names, including mucus protease inhibitor, antileukoprotease, bronchial secretory inhibitor, human seminal inhibitor I, cervix uteri secretion inhibitor, and secretory leukoprotease inhibitor (32, 56). The physiologic concentration of SLPI in saliva is 0.1 to 10 μg/ml (25, 40, 42, 57).

ANTIPROTEASE AND ANTI-INFLAMMATORY ACTIVITIES

The main function of SLPI is to protect local tissue against the detrimental consequences of inflammation. Indeed, a plethora of toxic (inflammatory) products, i.e., serine proteinases, is released from stimulated leukocytes during inflammation, and subsequent degradation of the tissues ensues. SLPI protects the tissues by inhibiting the proteases, such as cathepsin G, elastase, and trypsin from neutrophils; chymotrypsin and trypsin from pancreatic acinar cells; and chymase and tryptase from mast cells (12, 15, 20). Based on enzyme kinetic studies, its major physiologic function is probably the inhibition of neutrophil elastase (46, 53, 56). Neutrophil elastase as well as mast cell proteolytic enzymes can cause extensive tissue degradation and has been shown to be involved in several diseases, such as cystic fibrosis, non-cystic fibrosis bronchectasis, emphysema, acute respiratory distress syndrome, chronic bronchitis, and bacterial pneumonia (16, 44, 52).

SLPI exerts its antiprotease activity by means of its COOH-terminal domain (C-terminal domain), and the active center of which is formed by the Leu^{72}-Met^{73} residues (7, 55, 56). The NH_2-terminal domain (N-terminal domain) has no such properties, but it may aid in stabilizing the protease-antiprotease complex and may mediate the enhancement of the antiproteinase activity of SLPI by heparin (14, 60). Heparin augments the effectiveness of SLPI as it induces a conformational change in the inhibitor (24). In addition, SLPI increases glutathione levels, thereby reducing oxidant-mediated tissue injury, and prostaglandin E_2 and matrix metalloproteinases are reduced (13, 61). Hiemstra et al. hypothesized that SLPI's cysteine residues are utilized for the glutathione synthesis (17).

It is generally postulated that the balance between proteinases and antiproteinases is a prerequisite for the maintenance of tissue integrity (23). Indeed, it is shown that cleavage of SLPI results in increased tissue damage (13).

SLPI also shields the tissues against inflammatory products

* Corresponding author. Mailing address: Department of Oral Medicine/Pathology, Dental School, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece. Phone: 2310999524. Fax: 2310476366. E-mail: kdeod@cieel.gr.

by down-regulating the macrophage responses against bacterial lipopolysaccharides (LPS). LPS seem to induce SLPI production by macrophages directly or by way of interleukin-1β (IL-1β), tumor necrosis factor alpha, IL-6, and IL-10 (12, 20). SLPI in turn inhibits the downstream portion of the nuclear factor κB (NF-κB) pathway by protecting I-κβ (inhibiting factor of NF-κB) from degradation by the ubiquitin-proteosome pathway. Thus, SLPI renders macrophages unable to release proinflammatory cytokines and nitric oxide (16, 20). Ding et al. point out that the inhibitory effect of SLPI on macrophage responses may be due to its blockade of LPS transfer to soluble CD14 (receptor of macrophages) and its interference with the uptake of LPS from LPS-soluble CD14 complexes by macrophages (5). Nakamura et al. suggest that SLPI attenuates macrophages' responsiveness by inhibiting the LPS pathway through suppression of NF-κB and activation of CCAAT β enhancer-binding protein-transcription (29). In contrast, Sano et al. recently found that SLPI may up-regulate the LPS-induced activation of NF-κB in terms of transcriptional function (36). Finally, SLPI along with other factors manifests its anti-inflammatory profile by decreasing the C5a-related chemotactic activity (12). Thus, the accumulation of SLPI in the local tissue environment may represent an intrinsic feedback inhibition mechanism.

BACTERICIDAL AND ANTIFUNGAL ACTIVITIES

Although there are only a few published studies pertinent to this field, recent scientific evidence suggests that SLPI has broad-spectrum antibiotic activity that includes bactericidal and antifungal properties. In a recent study, Fahey and Wira (8) examined the production of antibacterial factor(s) by uterine epithelial cells from pre- and postmenopausal women. Apical rinse fluids from polarized epithelial cells recovered from women at the proliferative and secretory stages of the menstrual cycle were equally effective in killing *Staphylococcus aureus* and *Escherichia coli*, but those from postmenopausal women were not. SLPI concentrations in apical wash fluids from premenopausal women were significantly higher than those in wash fluids obtained from postmenopausal women. SLPI production correlated with bactericidal activity with respect to menstrual status and culture time. Anti-SLPI significantly decreased bactericidal activity of premenopausal epithelial cell rinse fluids. The endometrial epithelial cell line HEC-1A did not have a bactericidal effect, nor did it produce SLPI. In contrast, HEC-1B cells produced SLPI and a factor that inhibited bacterial growth. It seems that the N-terminal domain is responsible for the dose-dependent bactericidal properties of SLPI against both gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacteria. Hiemstra et al. showed that the activity of this domain is not as efficient as the one of the intact molecule. Hence, they speculated that a conformational change in the N-terminal domain is induced by the cleavage procedure of the native protein (17). In addition, Miller et al. suggested that the mechanism of the SLPI-mediated bactericidal activity may include binding of the protease inhibitor to the bacterial mRNA and DNA, but Hiemstra et al.'s findings proved that this binding is not enough to explain the antibacterial activity of SLPI (17, 27). The antiprotease domain of SLPI seems to play a crucial role in regulating host defense against infections by (i) inhibiting the elastase-mediated degradation of opsonins and receptors involved in phagocytosis and (ii) controlling the proteolytic processing of antimicrobial peptides, such as cathelicidins (16, 17).

Tomee and coworkers (51) showed that SLPI has activity (50% fungicidal activity) against human isolates of the pathogenic fungi *Aspergillus fumigatus* and *Candida albicans*. They also found partial inhibition of fungal protease activity by recombinant SLPI (rSLPI), a putative virulence factor of *A. fumigatus*, and subsequent inhibition of the inductive proinflammatory cytokine response in cultured human airway epithelial cell lines. In a recent study, Chattopadhyay and coworkers (4) showed that the increase of salivary SLPI levels (to >2.1 μg/ml) along with other factors, such as low levels of CD4, antiretroviral monotherapy, and smoking, is a key predictor of oral candidiasis in human immunodeficiency virus type 1 (HIV-1)-infected persons. A possible biological explanation for this association is that SLPI is up-regulated in response to the infection in order to kill the pathogen and resolve the disease. An individual threshold limit to SLPI production and secretion may be reached. Under this condition, the oral defenses are overwhelmed by the fungal insult and clinical disease ensues. In this scenario, an increase in salivary SLPI is associated with greater odds of having oral candidiasis and thus may be a marker of oral fungal disease. SPLI may also serve as an indicator of previous oropharyngeal candidiasis infection in the latter. Shugars et al. found that salivary SLPI concentrations diminish with aging. Hence, the proclivity of the elderly toward oral fungal infections may, in part, be due to reduced salivary SLPI levels compared to those in younger adults (43).

As with the antibacterial-bactericidal activity, the antifungal activity was mainly localized in the NH_2-terminal domain. It is believed that killing of fungus protects the epithelia from the fungal proteases (51). Probably the antibacterial and antifungal activities are related to the cationic nature of SLPI (52).

Given its antimicrobial activity, SLPI may provide a valuable therapeutic option in the future treatment or prevention of infectious diseases (52).

ANTI-HIV-1 ACTIVITY

SLPI is likely to be a major deterrent of HIV-1 transmission through oral secretions (3, 40). There is compelling evidence that although mucosae account for the most easily accessed route of HIV-1 transmission, paradoxically, the oral cavity is an infrequent route of transmission. SLPI was found to be the most potent anti-HIV-1 factor among several innate inhibitory molecules, namely, virus-specific antibodies, mucins, and thrombospondins, identified and purified from saliva (25). Moderate activity is also exerted against HIV-2 strains, but only when the concentration of SLPI exceeds the norm (40).

The anti-HIV-1 activity of SLPI was thoroughly investigated by numerous scientists. In 1995, McNeely and coworkers showed that infection of adherent primary monocytes with HIV-1 was significantly suppressed in the presence of human saliva. Of the proteins present in the saliva, only SLPI was found to have antiretroviral activity at physiological concentrations (0.1 to 10 μg/ml) (25). Since then, other reports have demonstrated that SLPI hampers HIV-1 infection of adherent monocytes (19, 26, 39, 41, 45, 57), although Turpin et al.

reported contradictory results (54). Konopka et al. also reported contradictory results, but that group subsequently reported confirmatory results obtained using their own source of rSLPI (22, 39). These discrepancies are attributed to either changes during synthesis of rSLPI molecules or differences in the intrinsic properties of the target cells, such as isolation, culture, and infection conditions; donor variations; and levels of macrophage maturation at the time of infection (22, 39). In addition, four in vitro studies have demonstrated SLPI anti-HIV-1 activity in nonmacrophage cells that included peripheral blood mononuclear cells, purified primary T cells, and SupT1 cells, a lymphocyte-derived tumor cell line (19, 25, 41, 45).

We should also point out that despite the potent anti-HIV-1 activity of SLPI, no activity against either other retroviruses, such as murine leukemia virus, human T-lymphotropic virus, and simian immunodeficiency virus, or unrelated viruses, such as cytomegalovirus and herpes simplex virus, has been demonstrated (42, 45, 57).

The mechanism by which SLPI inhibits HIV-1 infection is still elusive, but it appears to involve the host cell target rather than binding to the virus (25, 26, 45, 54). Moreover, SLPI's antiviral activity appears to be distinct from its known antiprotease activity (26). Evidence suggests that SLPI blocks HIV-1 internalization in a dose-dependent manner rather than binding to CD4 (26). McNeely et al. found that SLPI most likely inhibits a step of viral infection that occurs after virus binding but before reverse transcription. They also succeeded in preventing HIV infection of macrophages after pretreatment with SLPI. In the same report, they describe coprecipitation of a 55-kDa cell surface protein from monocytes by using anti-SLPI antibodies, but the identity of the putative SLPI receptor has not yet been determined (26). Chemokine receptor CCR5 was recently identified as the major coreceptor for the entry of macrophagetropic strains of HIV-1 (6). Naif et al. found that changes in CCR5 expression correlate with the susceptibility of macrophages to the productive infection and this interaction between HIV and CCR5 could be the main target of SLPI (28). Finally, Skott et al. reported diminished SLPI anti-HIV-1 activity with HIV-1 isolates having broad coreceptor usage patterns compared to that with isolates using solely CXCR4 or CCR5. This finding was also applied to explain the weakness of low concentrations of SLPI in inhibiting HIV-2 (45)

CONCLUSION

The present review suggests a multifaceted role for SLPI. Indeed, SLPI confers local protection against microbial, fungal, and HIV-1 insults. It is noteworthy that of the proteins present in the saliva only SLPI was found to have antiretroviral activity (anti-HIV-1 activity) at physiological concentrations. This fact partly explains the paucity of HIV-1 transmission via the oral route. SLPI also contributes to the confinement of tissue damage performed by the mechanisms of inflammation, thereby precipitating wound healing. Finally, SLPI is used as a marker to monitor the progress of an infection or a malignant lesion.

REFERENCES

1. **Abe, T., N. Kobayasi, and K. Yoshimura.** 1991. Expression of the secretory leukoprotease inhibitor gene in epithelial cells. J. Clin. Investig. **87:**2207–2215.
2. **Ashcroft, G. S., K. Lei, and W. Jin.** 2000. Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing. Nat. Med. **6:**1147–1153.
3. **Challacombe, S. J., and S. P. Sweet.** 2002. Oral mucosal immunity and HIV infection: current status. Oral Dis. **8**(Suppl. 2)**:**S55–S62.
4. **Chattopadhyay, A., L. R. Gray, L. L. Patton, and D. J. Caplan.** 2004. Salivary secretory protease inhibitor and oral candidiasis in human immunodeficiency virus type 1-infected persons. Infect. Immun. **72:**1956–1963.
5. **Ding, A., N. Thieblemont, and J. Zhu.** 1999. Secretory leukocyte protease inhibitor interferes with uptake of lipopolysaccharide by macrophages. Infect. Immun. **67:**4485–4489.
6. **Dragic, T., V. Litwin, G. P. Allaway, S. R. Martin, Y. Huang, and K. A. Nagashima.** 1996. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature **381:**667–673.
7. **Eisenberg, S. P., K. K. Hale, P. Heimdal, and R. C. Thompson.** 1990. Location of the protease-inhibitory region of secretory leukocyte protease inhibitor. J. Biol. Chem. **265:**7976–7981.
8. **Fahey, J. V., and C. R. Wira.** 2002. Effect of menstrual status on antibacterial activity and secretory leukocyte protease inhibitor production by human uterine epithelial cells in culture. J. Infect. Dis. **185:**1606–1613.
9. **Farquhar, C., T. C. VanCott, D. A. C. Mbori-Ngacha, L. Horani, R. K. Bosire, J. K. Kreiss, B. A. Richardson, and G. C. John-Stewart.** 2002. Salivary secretory leukocyte protease inhibitor is associated with reduced transmission of human immunodeficiency virus type 1 through breast milk. J. Infect. Dis. **186:**1173–1176.
10. **Franken, C., C. J. L. M. Meijer, and J. H. Dijkman.** 1989. Tissue distribution of antileukoprotease and lysozyme in humans. J. Histochem. Cytochem. **37:**493–498.
11. **Garver, R. I., K. T. Goldsmith, and B. Rodu.** 1994. Strategy for achieving selective killing of carcinomas. Gene Ther. **1:**46–50.
12. **Gipson, T. S., N. M. Bless, and T. P. Shanley.** 1999. Regulatory effects of endogenous protease inhibitors in acute lung inflammatory injury. J. Immunol. **162:**3653–3662.
13. **Greene, C., C. Taggart, and G. Lowe.** 2003. Local impairment of antineutrophil elastase capacity in community-acquired pneumonia. J. Infect. Dis. **188:**769–776.
14. **Grutter, M. G., G. Frendrich, R. Huber, and W. Bode.** 1988. The 2.5 Å X-ray crystal structure of the acid-stable proteinase inhibitor from human mucous secretions analysed in its complex with bovine alpha-chymothrypsin. EMBO J. **7:**345–351.
15. **He, S. H., P. Chen, and H. Q. Chen.** 2003. Modulation of enzymatic activity of human mast cell tryptase and chymase by protease inhibitors. Acta Pharm. Sin. **24:**923–929.
16. **Hiemstra, P. S.** 2000. Novel roles of protease inhibitors in infection and inflammation. Biochem. Soc. Trans. **30:**116–120.
17. **Hiemstra, P. S., R. J. Maassen, and J. Stolk.** 1996. Antibacterial activity of antileukoprotease. Infect. Immun. **64:**4520–4524.
18. **Hochstrasser, K., R. Reichert, S. Schwartz, and E. Werle.** 1972. Isolation and characterisation of a protease inhibitor from human bronchial secretion. Hoppe-Seyler's Z. Physiol. Chem. **353:**221–226.
19. **Hocini, H., P. Becquart, B. Hicham, A.-B. Homa, M. D. Kazatchkine, and L. Belec.** 2002. Secretory leukocyte protease inhibits infection of monocytes and lymphocytes with human immunodeficiency virus type 1 but does not interfere with cell-associated virus across tight epithelial barriers. Clin. Diagn. Lab. Immunol. **7:**515–518.
20. **Jin, F., C. Nathan, D. Radzioch, and A. Ding.** 1997. Secretory leukocyte protease inhibitor: a macrophage product induced by and antagonistic to bacterial lipopolysaccharide. Cell **88:**417–426.
21. **Kikushi, T., T. Abe, and S. Hoshi.** 1998. Structure of the murine secretory leukoprotease inhibitor (Slpi) gene and chromosomal localization of the human and murine SLPI genes. Am. J. Respir. Cell Mol. Biol. **19:**875–880.
22. **Konopka, K., N. Shine, E. Pretzer, and N. Düzgünes.** 1999. Secretory leukocyte protease inhibitor (SLPI): oxidation of SLPI does not explain its variable anti-HIV activity. J. Dent. Res. **78:**1773–1776.
23. **Kramps, J. A., C. Franken, and J. H. Dijkman.** 1988. Quantity of antileucoprotease relative to a1-proteinase inhibitor in peripheral airspaces of human lung. Clin. Sci. **75:**351–353.
24. **Marone, G., L. M. Lichtenstein, and S. J. Galli.** 2000. Regulation by physiological inhibitors, p. 278–279. *In* G. Marone, L. M. Lichtenstein, and S. J. Galli (ed.), Mast cells and basophils. Academic Press, San Diego, Calif.
25. **McNeely, T. B., M. Dealy, and D. J. Dripps.** 1995. Secretory leukocyte protease inhibitor: a human saliva protein exhibiting anti-human immunodeficiency virus 1 activity in vitro. J. Clin. Investig. **96:**456–464.
26. **McNeely, T. B., D. C. Shugars, M. Rosendahl, C. Tucker, S. P. Eisenberg, and S. M. Wahl.** 1997. Inhibition of human immunodeficiency virus type 1 infectivity by secretory leucocyte protease inhibitor occurs prior to viral reverse transcription. Blood **90:**1141–1149.

27. **Miller, K. W., R. J. Evans, S. P. Eisenberg, and R. C. Thompson.** 1989. Secretory leukocyte protease inhibitor binding to mRNA and DNA as a possible cause of toxicity to *Escherichia coli*. J. Bacteriol. **171:**2166–2172.
28. **Naif, H. M., S. Li, M. Alali, and A. Sloane.** 1998. CCR5 expression correlates with susceptibility of maturing monocytes to human immunodeficiency virus type 1 infection. J. Virol. **72:**830–836.
29. **Nakamura, A., Y. Mori, K. Hagiwara, and T. Suzuki.** 2003. Increased susceptibility to LPS-induced endotoxin shock in secretory leukoprotease inhibitor (SLPI)-deficient mice. J. Exp. Med. **197:**669–674.
30. **Nystrom, M., M. Bergenfeldt, I. Ljungcrantz, A. Lindeheim, and K. Ohlsson.** 1999. Production of secretory leukocyte proteinase inhibitor (SLPI) in human pancreatic beta-cells. Mediat. Inflamm. **8:**147–151.
31. **Odaka, C., T. Mizuochi, J. Yang, and A. Ding.** 2003. Murine macrophages produce secretory leukocyte protease inhibitor during clearance of apoptotic cells: implications for resolution of the inflammatory response. J. Immunol. **171:**1507–1514.
32. **Ogra, P. I., J. Mestecky, and M. E. Lamm.** 1999. Proteinase inhibitors, p. 97. *In* P. I. Ogra, J. Mestecky, and M. E. Lamm (ed.), Mucosal immunology, 2nd ed. Academic Press, San Diego, Calif.
33. **Ohlsson, K., and H. Tegner.** 1976. Inhibition of elastase from granulocytes by the low molecular weight bronchial protease inhibitor. Scand. J. Clin. Lab. Investig. **36:**437–445.
34. **Ohlsson, S., I. Ljungkrantz, K. Ohlsson, M. Seyelmark, and J. Wieslander.** 2001. Novel distribution of the secretory leucocyte proteinase inhibitor in kidney. Mediat. Inflamm. **10:**347–350.
35. **Pillay, K., A. Coutsoudis, and A. K. Agadzi-Naqvi.** 2001. Secretory leukocyte protease inhibitor in vaginal fluids and perinatal human immunodeficiency virus type 1 transmission. J. Infect. Dis. **183:**653–656.
36. **Sano, C., T. Shimizu, and H. Tomioka.** 2003. Effects of secretory leukocyte protease inhibitor on the tumor necrosis factor-alpha production and NF-kB activation of lipopolysaccharide-stimulated macrophages. Cytokine **21:**38–42.
37. **Schalkwijk, J., O. Wiedow, and S. Hirose.** 1999. The trappin gene family: proteins defined by an N-terminal transglutaminase substrate domain and a C-terminal four-disulphide core. Biochem. J. **340:**569–577.
38. **Seemüller, U., M. Arnold, and H. Fritz.** 1986. The acid-stable proteinase inhibitor of human mucous secretions (HUSI-1, antileucoprotease). FEBS Lett. **199:**43–48.
39. **Shine, N. R., S. C. Wang, K. Konopka, E. A. Burks, N. Düzgünes, and C. P. Whitman.** 2002. Secretory leukocyte protease inhibitor: inhibition of human immunodeficiency virus-1 infection of monocytic THP-1 cells by a newly cloned protein. Bioorg. Chem. **30:**249–263.
40. **Shugars, D. C.** 1999. Endogenous mucosal antiviral factors of the oral cavity. J. Infect. Dis. **179**(Suppl. 3)**:**s431–s435.
41. **Shugars, D. C., D. L. Sauls, and J. B. Weinberg.** 1997. Secretory leukocyte protease inhibitor blocks of primary monocytes and mononuclear cells with both monocytotropic and lymphocytotropic strains of human immunodeficiency virus type I. Oral Dis. **3**(Suppl. 1)**:**S70–S72.
42. **Shugars, D. C., A. L. Alexander, K. Fu, and S. A. Freel.** 1999. Endogenous salivary inhibitors of human immunodeficiency virus. Arch. Oral Biol. **44:**445–453.
43. **Shugars, D. C., C. A. Watkins, and H. J. Cowen.** 2001. Salivary concentration of secretory leukocyte protease inhibitor, an antimicrobial protein, is decreased with advanced age. Gerontology **47:**246–253.
44. **Simpson, A. J., W. A. H. Wallace, and M. E. Marsden.** 2001. Adenoviral augmentation of elafin protects the lung against acute injury mediated by activated neutrophils and bacterial infection. J. Immunol. **167:**1778–1786.
45. **Skott, P., E. Lucht, M. Ehnlund, and E. Björling.** 2002. Inhibitory function of secretory leukocyte proteinase inhibitor (SLPI) in human saliva is HIV-1 specific and varies with virus tropism. Oral Dis. **8:**160–167.
46. **Smith, C. E., and D. A. Johnson.** 1985. Human bronchial leucocyte proteinase inhibitor. Biochem. J. **225:**463–472.
47. **Sorensen, O. E., J. B. Cowland, K. Theilgaard-Monch, L. Liu, T. Ganz, and N. Borregaard.** 2003. Wound healing and expression of antimicrobial peptides/polypeptides in human keratinocytes, a consequence of common growth factors. J. Immunol. **170:**5583–5589.
48. **Stetler, G., M. T. Brewer, and R. C. Thompson.** 1986. Isolation and sequence of a human gene encoding a potent inhibitor of leukocyte proteases. Nucleic Acids Res. **14:**7883–7896.
49. **Tegner, H.** 1978. Quantification of human granulocyte protease inhibitors in non-purulent bronchial lavage fluids. Acta Oto-Laryngol. **85:**282–289.
50. **Thompson, R. C., and K. Ohlsson.** 1988. Isolation, properties, and complete amino acid sequence of human secretory leucocyte protease inhibitor, a potent inhibitor of leukocyte elastase. Proc. Natl. Acad. Sci. USA **83:**6692–6696.
51. **Tomee, J. F. C., P. S. Hiemstra, R. Heinzel-Wieland, and H. F. Kauffman.** 1997. Antileukoprotease: an endogenous protein in the innate mucosal defense against fungi. J. Infect. Dis. **176:**740–747.
52. **Tomee, J. F. C., G. H. Kolter, P. S. Hiemstra, and H. F. Kauffman.** 1998. Secretory leucoprotease inhibitor: a native antimicrobial protein presenting a new therapeutic opinion? Thorax **53:**114–116.
53. **Travis, J., and H. Fritz.** 1991. Potential problems in designing elastase inhibitors for therapy. Am. Rev. Respir. Dis. **143:**1412–1415.
54. **Turpin, J. A., C. A. Schaeffer, and M. Bu.** 1996. Human immunodeficiency virus type-1 (HIV-1) replication is unaffected by human secretory leukocyte inhibitor. Antivir. Res. **29:**269–277.
55. **Van-Seuringen, I., and M. Davril.** 1991. Separation of the two domains of human mucus proteinase inhibitor: inhibitory activity is only located in the carboxy-terminal domain. Biochem. Biophys. Res. Commun. **179:**1587–1592.
56. **Vogelmeier, C., A. Gillissen, and R. Buch.** 1996. Use of secretary leukoprotease inhibitor to augment lung antineutrophil elastase activity. Chest **110:**261s–266s.
57. **Wahl, S. M., T. B. McNeely, and E. N. Janoff.** 1997. Secretory leukocyte protease inhibitor (SLPI) in mucosal fluids inhibits HIV. Oral Dis. **3**(Suppl. 1)**:**S64–S69.
58. **Wang, X., X. Li, and L. Xu.** 2003. Up-regulation of secretory leukocyte protease inhibitor (SLPI) in the brain after ischemic stroke: adenoviral expression of SLPI protects brain from ischemic injury. Mol. Pharmacol. **64:**833–840.
59. **Westin, U., M. Nyström, I. Ljungcrantz, B. Eriksson, and K. Ohlsson.** 2002. The presence of elafin, SLPI, IL1-RA and STNFα in head and neck squamous cell carcinomas and their relation to the degree of tumor differentiation. Mediat. Inflamm. **11:**7–12.
60. **Ying, Q. L., M. Kemme, and S. R. Simon.** 1994. Functions of the N-terminal domain of secretory leukoprotease inhibitor. Biochemistry **33:**5445–5450.
61. **Zang, Y., D. L. De Witt, T. B. McNeely, S. M. Wahl, and L. M. Wahl.** 1997. Secretory leukocyte protease inhibitor suppresses the production of monocyte prostaglandin H synthase-2, prostaglandin E2, and matrix metalloproteases. J. Clin. Investig. **99:**894–900.

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