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Secretory Leukocyte Protease Inhibitor (SLPI) in mucosal tissues: Protects against inflammation, but promotes cancer

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ABSTRACT

The immune system is continuously challenged with large quantities of exogenous antigens at the barriers between the external environment and internal human tissues. Antimicrobial activity is essential at these sites, though the immune responses must be tightly regulated to prevent tissue destruction by inflammation. Secretory Leukocyte Protease Inhibitor (SLPI) is an evolutionarily conserved, pleiotropic protein expressed at mucosal surfaces, mainly by epithelial cells. SLPI inhibits proteases, exerts antimicrobial activity and inhibits nuclear factor-kappa B (NF-κB)-mediated inflammatory gene transcription. SLPI maintains homeostasis at barrier tissues by preventing tissue destruction and regulating the threshold of inflammatory immune responses, while protecting the host from infection. However, excessive expression of SLPI in cancer cells may have detrimental consequences, as recent studies demonstrate that overexpression of SLPI increases the metastatic potential of epithelial tumors. Here, we review the varied functions of SLPI in the respiratory tract, skin, gastrointestinal tract and genitourinary tract, and then discuss the mechanisms by which SLPI may contribute to cancer.

1. SLPI structure, functions and regulation

1.1. Structure

SLPI is expressed in various human epithelia, including the salivary glands, the epidermis of the skin and the epithelia that line the respiratory, gastrointestinal and genitourinary tracts [1–6]. SLPI initially had several tissue-specific names (see Box 1); however, in 1988, these proteins were proven to be identical and encoded by a single gene in the human genome [7]. The SLPI protein has a boomerang-like shape and contains two domains with similar architecture, with the polypeptide segments of each domain connected by four disulphide bridges [8]. SLPI is a member of the whey-acidic protein (WAP) family, which all contain four-disulphide core domains [9]. The gene encoding SLPI is evolutionarily conserved across birds, reptiles and mammals [10,11]. Human and murine SLPI are 68% homologous at the genomic level and 60% homologous at the protein level [12–14], though the protease binding site and protease inhibitory capacity differ between species [15,16].

1.2. Functions

1.2.1. Prevention of tissue destruction

SLPI strongly inhibits serine proteases, including neutrophil elastase [5,17]. Leukocytes secrete proteases to facilitate their migration through the extracellular matrix of tissues and to kill phagocytosed microorganisms. Endogenous protease inhibitors counteract the action of these proteases to limit collateral tissue damage. Some protease inhibitors are produced by the liver ('systemic antiproteases'), while others are produced locally and upregulated by bacterial products and inflammatory cytokines ('alarm antiproteases') [18]. SLPI and Elafin (also known as peptidase inhibitor 3 or skin-derived antileukoprotease) are two well-characterized human alarm antiproteases.

The region responsible for the protease inhibitory activity of SLPI is located on its C-terminal domain [8,19,20]. SLPI is the major inhibitor of neutrophil elastase in the cytoplasm of neutrophils [21] and is the only elastase inhibitor that has been identified in saliva [22]. SLPI retains its capacity to inhibit neutrophil elastase when cross-linked to fibronectin or elastin by tissue transglutaminase-2 and plasma factor XIIIa [23]. In addition, SLPI inhibits the production of matrix metalloproteinases (MMPs) by monocytes [24] and can also prevent the formation of

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Box 1
What is SLPI?

- Low-molecular-weight (11,726 Daltons) 107-amino acid non-glycosylated protein [5,195,196]
- The human *SLPI* gene is located on chromosome 20q12 13.2 [9,14]
- Official name: Secretory Leukocyte Protease Inhibitor; alternative names: human seminal plasma inhibitor I, cervix uteri secretion inhibitor, bronchial secretory inhibitor, bronchial mucus inhibitor, bronchial leukocyte proteinase inhibitor, anti-leukoprotease
- Member of the WAP family, of which SLPI and Elafin are most-well studied [9]
- Produced by human epithelial cells, macrophages, neutrophils and mast cells [21,53–55]
- Produced by murine epithelial cells, macrophages, neutrophils, mast cells, germinal center B cells and innate lymphoid cells (The Immunological Genome Project; [197]
- Present in high concentrations in a variety of secretions, including saliva and nasal, bronchial, intestinal and cervical mucus [1,5,59,60]
- Can rapidly cross membranes and most likely does not need a receptor to enter cells [29]
- Identified functions include:
  - o Inhibits serine proteases, including neutrophil elastase, cathepsin G, chymotrypsin, trypsin and chymase [5,20,70,198]; SLPI belongs to the chelonianin family of serine protease inhibitors [17]
  - o Inhibits TLR signaling by inhibiting uptake of lipopolysaccharide (LPS) and inhibiting NF-κB signaling [26,28,29]
  - o Antimicrobial protein: exerts antibacterial and antifungal activity and prevents HIV-1 transmission [2,36,38,199]
  - o Differentiation and survival factor for $CD34^+$ bone marrow hematopoietic progenitors [51]
  - o Anticoagulant [52,150]

neutrophil extracellular traps (NET) [25]. Overall, SLPI contributes to local tissue homeostasis by preventing damage by innate immune cells.

1.2.2. Regulation of inflammation

As well as counteracting the effects of proteases produced by innate immune cells, SLPI can also prevent the production of pro-inflammatory cytokines and the subsequent recruitment of immune cells. SLPI inhibits Toll-like receptor (TLR) signaling at three levels: extracellular SLPI interferes with the binding of LPS to soluble CD14 and the movement of LPS from CD14 into cell membranes [26]; cytosolic SLPI prevents degradation of the NF-κB inhibitor alpha (IκBα) [27] to attenuate TLR2 and TLR4 signaling [28]; and, in the nucleus, SLPI competes with p65 for NF-κB consensus-binding sites, and thereby directly prevents p65 binding NF-κB [29]. The ability of SLPI to inhibit NF-κB signaling is independent of the anti-protease activity of the protein, as amino acid substitutions in the C-terminal domain that disrupt the anti-protease function of SLPI do not affect LPS-induced nitric oxide and tumor necrosis factor alpha (TNF-α) production by macrophages [30].

By inhibiting NF-κB signaling, SLPI shifts the balance of cellular cytokine production by suppressing production of proinflammatory cytokines by activated monocytes (TNF-α; IL-8) [29], dendritic cells (DCs; TNF-α; IL12p70) [31,32], macrophages (TNF-α; nitric oxide) [12] and epithelial cells (IL-8) [33]. In turn, SLPI-induced modulation of monocyte function inhibits adaptive $CD4^+$ T helper cell proliferation and suppresses secretion of cytokines by T helper type 1 (Th1) cells, but does not alter $CD8^+$ cytotoxic T cell proliferation *in vitro* [34]. SLPI also achieves selective $CD4^+$-Th1 suppression by increasing the production of IL-4, IL-6 and IL-10 by monocytes in the presence of T cell-derived IL-2 [34].

SLPI also indirectly regulates $CD4^+$ T cells *in vivo* via DCs. Specifically, in the lymph nodes draining the nasal mucosa, expression of SLPI in DCs attenuates the release of microbiota-induced IL-12p70, monocyte chemoattractant protein 1 (MCP1) and IL-6, thereby maintaining T cell-mediated mucosal tolerance to harmless proteins encountered at the densely colonized nasal mucosal surface [32]. In addition, SLPI produced by tonsillar epithelial cells suppresses immunoglobulin class switching in activated B cells by inhibiting NF-κB signaling [35].

Overall, SLPI prevents the production of several pro-inflammatory cytokines and indirectly attenuates adaptive inflammatory immune responses, and thereby maintains balanced immune responses at mucosal barrier tissues.

1.2.3. Antimicrobial activity

SLPI also possesses broad-spectrum antibacterial, antifungal and antiviral properties [2,36–38]. SLPI can directly kill *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Candida albicans* and *Aspergillus fumigatus* [2,36–40]. In addition, SLPI is the only salivary protein that exerts activity against human immunodeficiency virus 1 (HIV-1) at physiological concentrations [41].

The N-terminal domain of SLPI possesses both antibacterial and antifungal activity, whereas the C-terminus exhibits low antibacterial activity [36,38]. Therefore, the antibacterial activity of SLPI is most likely independent of its antiprotease activity. However, the mechanisms by which SLPI kills microorganisms are not entirely clear. SLPI can bind to *Escherichia coli* bacterial mRNA and DNA, which inhibits translation and arrests bacterial growth [42]. In addition, the cationic nature of SLPI may allow the protein to attach to and destabilize the anionic cell membrane of bacteria [36,38]. SLPI can prevent transmission of HIV-1 via a mechanism independent of its antiprotease activity, as amino acid substitutions that reduce the protease inhibitor activity of SLPI do not affect its anti-HIV-1 activity [43]. SLPI binds to human macrophages via annexin II, a cofactor involved in HIV-1 infection, and thereby disrupts the interaction between HIV-1 and macrophages [44]. In addition, SLPI inhibits the interactions of the host membrane proteins phospholipid scramblase 1 and 4 with CD4, the main receptor for HIV-1 on T cells and macrophages [45].

Several microorganisms have evolved strategies to counteract the effects of SLPI. *Trichomonas vaginalis* secretes proteases that degrade SLPI [46] and *Streptococcus pyogenes* strains secrete streptococcal inhibitor of complement, which prevents bacterial cell killing induced by SLPI [40]. *Pseudomonas aeruginosa* enhances the cleavage and inactivation of recombinant SLPI by neutrophil elastase [47]. In addition, herpes simplex virus 1 and 2 are inhibited by SLPI and downregulate *SLPI* gene expression in human cervical epithelial cells [48].

1.2.4. Diverse functions of SLPI

Several recent studies uncovered novel functions for SLPI that still require further investigation. In particular, SLPI has been shown to inhibit apoptosis in human neutrophils and monocytes [49,50]. Moreover, SLPI has been reported to be essential for the differentiation and survival of human $CD34^+$ bone marrow hematopoietic progenitors [51]. However, detailed knowledge of the role of SLPI in myelopoiesis is lacking. In addition, SLPI may act as an anticoagulant. The plasma coagulation time is prolonged in *Slpi* knockout mice, despite normal thrombopoiesis [52], though it is not known whether SLPI acts as

Box 2
SLPI exerts varied functions, depending on the cellular location

- Extracellular:
  - o Inhibits proteases (summarized in [17])
  - o Inhibits uptake of LPS by macrophages [26]
  - o Kills bacteria and fungi [36,38]
- Cytoplasmic:
  - o Inhibits proteases
  - o Prevents degradation of IκBα and IRAK [28]
  - o Inhibits entry of HIV-1 into host cells [45]
- Nuclear:
  - o Directly blocks NF-κB binding sites in the nucleus [29]

anticoagulant in humans.

1.3. Regulation of SLPI expression, production and secretion

SLPI is expressed by human epithelial cells [53,54], neutrophils [21,55], macrophages [56], mast cells [57] and fibroblasts [58]. SLPI is secreted in saliva and mucus at high concentrations [1,5,59,60]; the concentration of SLPI in saliva is 30-fold higher than in serum [22]. Whether SLPI expression is regulated in a cell-type specific manner is unclear. In both epithelial and myeloid cells, *SLPI* mRNA is upregulated by a wide variety of TLR ligands and pattern recognition receptor ligands, such as Dectin-1 [12,31,33]. In addition, TNF-α, interleukin-1 beta (IL-1β), transforming growth factor alpha (TGF-α), insulin-like growth factor 1 (IGF-1), progesterone and corticosteroids are all reported to increase *SLPI* mRNA expression in epithelial cells [37,54,61–63]. Defensins increase the production of SLPI protein, but not mRNA expression, by epithelial cells [64]. In macrophages, *SLPI* mRNA expression is upregulated by IL-10 and IL-6 and downregulated by interferon-γ (IFN-γ) [12,65,66]. Interestingly, IFN-γ restores the production of TNF-α and nitric oxide in response to LPS by SLPI-expressing macrophages, suggesting IFN-γ can overrule SLPI-induced tolerance to LPS [12]. Furthermore, macrophages exposed to apoptotic cells secrete increased levels of SLPI, though the related mechanism is unknown [65]. Secretion of SLPI by neutrophils can be enhanced by stimulation with phorbol 12-myristate 13-acetate (PMA), but not by LPS or granulocyte-macrophage colony-stimulating factor (GM-CSF) [21]. Additionally, upregulation of SLPI in murine DCs occurs in the late stages after TLR stimulation and appears to be predominantly mediated by the MAPK pathway, rather than NF-κB signaling [31]. However, it is not known whether SLPI expression is regulated by the MAPK signaling pathway in other cell types. The exact mechanisms responsible for *de novo* induction and/or upregulation of SLPI are poorly defined.

Table 1
Main functions of SLPI at various barrier sites based on human and animal studies.

	Tissue repair	Anti-inflammatory activity	Anti-microbial activity
Respiratory tract	Prevents tissue destruction by inhibiting proteases (*in vitro* and *in vivo*) [75,76,113]	Reduces alveolitis via inhibition of NF-κB (*in vivo*) [108,109]; reduces allergic asthma (*in vivo*) [111,112]	Kills lung pathogens (*in vitro*) [2]
Skin	Promotes wound healing via protease inhibition and suppression of TGF-β (*in vivo*) [123]	Promotes wound healing via suppression of neutrophil recruitment (*in vivo*) [123,125]	Kills skin commensals and pathogens (*in vitro*) [2]
Gastrointestinal tract	Promotes oral wound healing via protease inhibition (*in vivo*) [141]; ameliorates intestinal tissue damage caused by proteases (*in vitro* and *in vivo*) [37,136,138]	Suppresses epithelial chemokine production in response to microbial antigens via NF-κB inhibition (*in vitro* and *in vivo*) [33]; maintains tolerance to harmless protein antigens encountered at microbiota-rich mucosal sites (*in vivo*) [32]	Kills intestinal pathogens (*in vitro*) [36,37]
Genitourinary tract	Unknown	Unknown	Prevents HIV-1 infection (*in vitro*) [199]; kills bacteria that cause lower urinary tract infections (*in vitro*) [2,144]

1.4. Inactivation of SLPI

Secreted SLPI can be inactivated by activated neutrophils via myeloperoxidase-catalyzed oxidation [67]. In addition, MMP-9 destroys SLPI by cleaving both its N-terminal and C-terminal domains, which decreases the ability of SLPI to inhibit neutrophil elastase and attenuates the LPS-responsiveness of monocytes [68]. Cleaved SLPI loses its capacity to suppress the production of MMP-9 by monocytes, suggesting that high production of MMP-9 can overrule SLPI [68]. Similar observations have been made for the protease chymase, which cleaves SLPI [69] and is also inhibited by SLPI [70]. Furthermore, cathepsin B, L and S can cleave SLPI, which inactivates its anti-neutrophil elastase activity [71]. SLPI itself inhibits IFN-γ-induced cathepsin S production by macrophages via inhibition of NF-κB [72]. Collectively, these data indicate a delicate balance exists between proteases and SLPI; this balance can shift towards inactivation of SLPI when the tissue is infiltrated by high numbers of innate immune cells, which may result in higher protease activity and tissue damage.

1.5. Conclusions

SLPI is produced by epithelial cells and immune cells, such as macrophages and neutrophils. Production of SLPI increases when these cells sense microorganisms through pattern recognition receptors or when stimulated by cytokines produced by innate immune cells. SLPI possesses a diverse range of functions, and intracellular and extracellular SLPI exert different effects (see Box 2). Importantly, SLPI protects against excessive inflammatory immune responses at epithelial barriers.

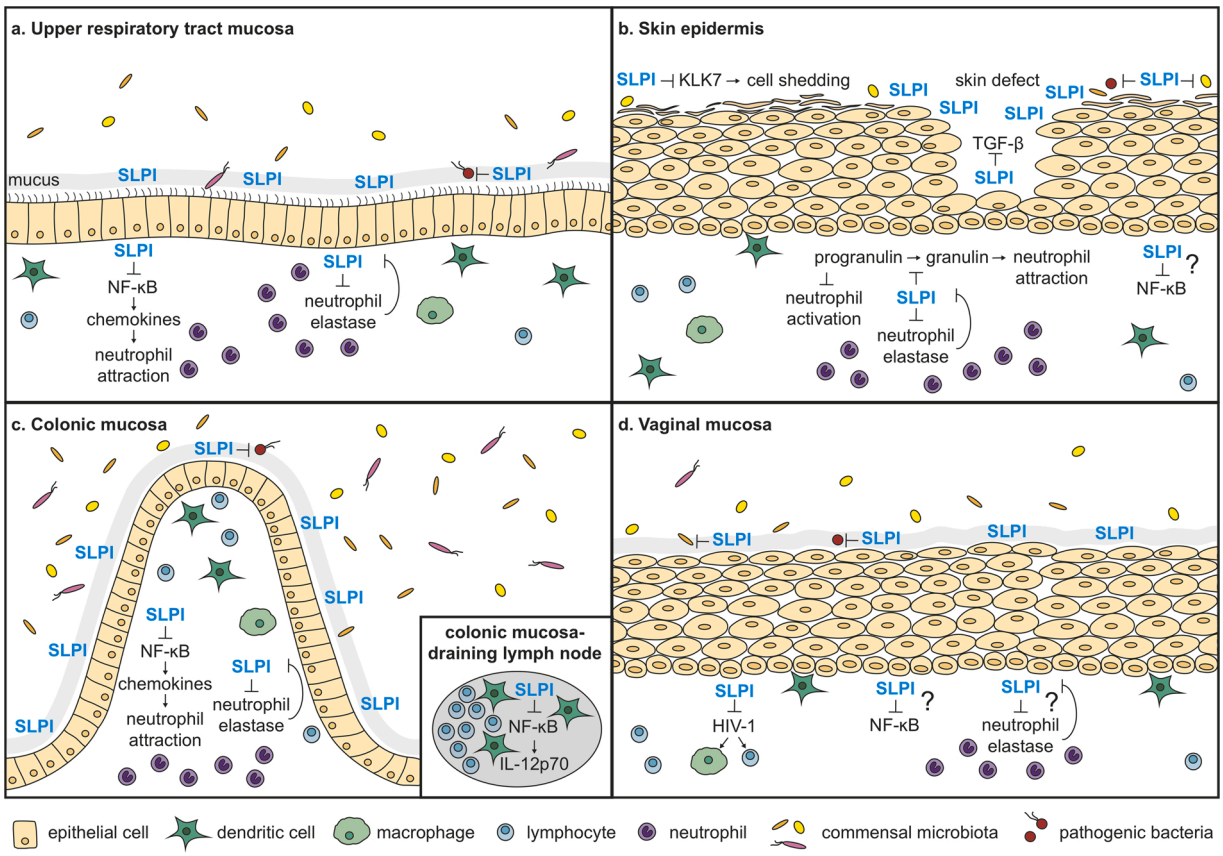

Fig. 1. SLPI maintains tissue homeostasis at various barrier tissues.
(a) In the mucosa of the upper respiratory tract, SLPI prevents tissue destruction by neutrophils via inhibition of neutrophil elastase. In turn, neutrophil elastase inactivates SLPI. In addition, SLPI inhibits the activation of epithelial NF-κB and thereby suppresses chemokine production and neutrophil attraction. SLPI also possibly kills pathogenic bacteria in the lung. (b) In the skin, SLPI inhibits keratinocyte shedding in the upper epidermis by inhibiting KLK7. SLPI is upregulated in keratinocytes after wounding. SLPI contributes to wound healing by inhibiting neutrophil elastase, inhibiting TGF-β and preventing conversion of the epithelial growth factor progranulin to granulin. Granulin promotes attraction of neutrophils by inducing production of chemokines by epithelial cells. Furthermore, SLPI can kill both skin commensals and pathogens. Whether SLPI inhibits NF-κB in keratinocytes is unclear. (c) In the colonic mucosa, SLPI suppresses epithelial cell production of chemokines by inhibiting activation of NF-κB in response to microbial contact. SLPI also inhibits neutrophil elastase in intestinal tissue. In addition, SLPI can kill intestinal pathogens. In mucosa-draining lymph nodes, SLPI prevents activation of DCs by inhibiting IL-12p70 production in response to microbial signals. (d) In the vaginal mucosa, SLPI prevents the entry of HIV-1 into macrophages and T cells and can kill bacteria and fungi. Whether SLPI inhibits NF-κB in the vaginal epithelium is unknown. Finally, inhibition of proteases by SLPI has not been studied in the female reproductive tract.

Moreover, secreted SLPI can be taken up by cells that do not express SLPI. Thus, the function of SLPI extends beyond the innate immune response.

One key function of SLPI is suppression of pro-inflammatory cytokine production, likely via a negative feedback mechanism, to prevent excessive inflammatory immune responses after microbial contact. This suggestion is supported by the finding that *Slpi* knockout mice are more sensitive to a breach of mucosal tolerance to harmless antigens in the presence of LPS [32] and to LPS-induced endotoxin shock compared to wild-type littermates [73]. However, SLPI is cleaved and inactivated in the presence of high numbers of activated innate immune cells. In addition, IFN-γ can inhibit SLPI production and possibly overrule SLPI-induced tolerance to LPS [12]. These findings lead to the question of whether SLPI retains its tissue-protective capacity during chronic inflammation.

Slpi knockout mice do not exhibit overt abnormalities under specific pathogen-free (SPF) conditions, which is remarkable in view of the crucial roles of SLPI in immune regulation, tissue healing, antimicrobial defense, hematopoiesis and coagulation [73]. These observations suggest that SLPI is only essential during tissue dysregulation, such as infection or chronic inflammation. As yet, no case reports of individuals with SLPI deficiencies have been described. However, the production of SLPI varies among healthy individuals [37], and it is unclear whether this variation is intrinsic or depends on environmental factors, such as microbial colonization.

2. SLPI at different barrier sites

The functions of SLPI have been studied in different tissues, in the context of various human diseases and using multiple animal models. Here, we discuss the roles of SLPI at the main barriers between the external environment and the body—the respiratory tract, skin, gastrointestinal tract and genitourinary tract (see Table 1 and Fig. 1)—focusing on tissue homeostasis and chronic inflammation.

2.1. SLPI in the respiratory tract

SLPI is produced in the lungs by bronchial epithelial cells, alveolar macrophages and neutrophils [4,21,56,74]. SLPI isolated from human bronchial secretions is a strong inhibitor of neutrophil elastase and accounts for the majority of the total molar concentration of neutrophil protease inhibitors in bronchoalveolar lavage (BAL) fluid [75–77]. SLPI is responsible for the majority of the anti-elastase activity in the upper respiratory tract; in contrast, in the peripheral airspaces, α_1-antitrypsin (A1AT) is more abundant and most SLPI protein is inactive [78–80]. *SLPI* mRNA is expressed at 30-fold higher levels in human airway

submucosal glands compared to the superficial epithelium [81]. Neutrophil elastase and defensins increase SLPI production in airway epithelial cells [82,83], whereas TGF-β inhibits SLPI production [84,85]. IL-1β and TNF-α upregulate SLPI expression in alveolar epithelial cells [54]. SLPI is also present and exclusively associated with elastin fibers in lung connective tissue, suggesting that SLPI protects these fibers against degradation by elastase [86].

The roles of SLPI in disease have been studied most extensively in the lungs. An imbalance between proteases and protease inhibitors contributes to lung destruction in chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) [87]. Chemotactic peptides are released when proteases break down collagen and elastin, resulting in accumulation of neutrophils and increased production of proteases [39,88,89]. In addition, neutrophil elastase stimulates respiratory epithelial cells to produce IL-8, a strong chemoattractant for neutrophils [90,91]. SLPI limits neutrophil-induced lung destruction by inhibiting neutrophil elastase and attenuating IL-8 production in bronchial epithelial cells [92,93]. However, as neutrophil elastase also inactivates SLPI, this protective effect can be lost when high levels of neutrophil elastase are present [64,80,94]. The sputum of patients with COPD contains higher levels of SLPI during acute exacerbations compared to patients with stable COPD or healthy individuals [95]. However, the BAL fluid of patients with COPD also contains higher levels of IFN-γ and cathepsins compared to healthy controls; which results in cleavage and inactivation of SLPI in the epithelial lining fluid of patients with emphysema, but not in healthy controls [71,72]. Thus, the insufficient amounts of SLPI in the sputum of patients with COPD fail to control the activity of neutrophil proteases, and this balance is disturbed even more during exacerbations [96]. Conventional treatment for severe acute COPD exacerbations results in an increase in the sputum SLPI concentration within 48 hours, suggesting recovery of this balance [97].

The concentrations of SLPI in BAL fluid are not different between patients with CF and healthy controls [98]. However, despite containing normal concentrations of SLPI, the lung epithelial lining fluid of children with CF contains higher concentrations of active neutrophil elastase [99]. In addition, patients with CF are often chronically infected with *Pseudomonas aeruginosa,* a bacterium that produces an elastase [100,101]. SLPI exerts antibacterial activity against *Pseudomonas aeruginosa* [2], but both neutrophil elastase and *Pseudomonas aeruginosa* are able to cleave and inactivate SLPI [47,80]. Indeed, patients with CF infected with *Pseudomonas aeruginosa* have lower SLPI levels and higher levels of neutrophil elastase in their BAL fluid compared to *Pseudomonas aeruginosa*-negative patients with CF [47,98]. Moreover, SLPI is cleaved in the lower airway secretions of patients with non-CF bronchiectasis [68]. In addition, in patients with allergic rhinitis and allergic asthma, the ratio of cleaved SLPI to total SLPI positively correlates with the concentration of chymase in nasal lavage fluid [102]. Taken together, this evidence indicates that the levels of active SLPI are insufficient to counteract the elevated production of proteases in chronic lung diseases.

These observations suggest that administration of SLPI could be beneficial in chronic lung diseases. Recombinant SLPI has been shown to inhibit IL-8-induced neutrophil chemotaxis and decrease degranulation of MMP-9, cathelicidin and myeloperoxidase by neutrophils [103]. Interestingly, higher concentrations of recombinant SLPI are needed to inhibit the chemotaxis of neutrophils isolated from patients with COPD or CF compared to neutrophils from healthy subjects [103]. Hypersecretion of mucus is a feature of both COPD and CF, and can be counteracted by recombinant SLPI *in vitro* [104]. Moreover, recombinant SLPI ameliorates the severity of disease in several animal models of COPD [105–108]. Interestingly, intratracheal administration of recombinant SLPI reduced lung damage in an IgG immune complex-induced model of acute alveolitis in rats, at least partially by inhibiting epithelial NF-κB signaling [108,109]. Inhibition of SLPI using a blocking antibody significantly increased lung injury in the same model, and was associated with abundant neutrophil accumulation [110]. In addition, overexpression of *Slpi* reduced the signs of asthma in two mouse models of allergic asthma [111,112]. Conversely, *Slpi* knockout mice developed more severe allergic asthma [112]. Aerosolization of recombinant SLPI was proven to inhibit neutrophil elastase activity in the airway epithelial lining fluid of healthy humans [113]. Aerosolized recombinant SLPI also reduced neutrophil elastase activity in airway epithelial lining fluid and reduced *IL8* mRNA expression in the bronchial epithelial cells of patients with CF [113–115]. However, aerosolized SLPI does not reach the poorly ventilated areas of the lungs in patients with CF or emphysema [116]. Moreover, hypoxia downregulates SLPI expression in bronchial epithelial cells [117]. More stable variants of SLPI that are less susceptible to neutrophil elastase degradation and oxidation—but still bind to LPS and inhibit NF-κB signaling—have been developed [118,119].

In conclusion, SLPI production maintains respiratory tract homeostasis by inhibiting proteases, suppressing chemokine production and exerting antibacterial activity. However, SLPI activity is insufficient to counteract the excessive production of proteases in chronic lung diseases.

2.2. SLPI in the skin

SLPI is expressed and upregulated by calcium in human keratinocytes [2,120]. The role of SLPI in the skin has been studied in the context of wound healing. Sterile wounding of human skin induces SLPI expression in keratinocytes via activation of the epidermal growth factor receptor (EGFR) by the growth factors IGF-1 and TGF-α [121,122]. SLPI is essential for cutaneous wound healing in mice [123,124]. *Slpi* knockout mice suffer delayed wound healing associated with increased elastase activity, accumulation of neutrophils and monocytes, and increased activation of TGF-β in the wounded skin [123]. Mice deficient in Slpi due to a deficiency in natural resistance-associated macrophage protein 1 (Nramp1) also suffer delayed wound healing associated with overexpression of TGF-β [124]. Interestingly, neutralization of TGF-β does not reverse the delayed wound healing in *Slpi* knockout mice as effectively as exogenous SLPI, suggesting that SLPI promotes wound healing viaadditional mechanisms beyond suppression of TGF-β alone [123]. Indeed, SLPI also promotes wound healing by preventing the conversion of progranulin to granulin peptides by neutrophil elastase. Progranulin is an epithelial growth factor that blocks the activation of neutrophils by TNF-α. In contrast, granulin peptides induce IL-8 secretion and thereby attract neutrophils. Crucially, progranulin restores wound healing in *Slpi* knockout mice [125]. Whether the antimicrobial activity of SLPI also promotes wound healing is unclear. SLPI is able to kill several microorganisms that can infect the skin [2]; however, the relevance of the antimicrobial activity of SLPI in the skin is unknown. SLPI may also prevent scarring after wound healing, as it inhibits excessive contraction of collagen gel by human fibroblasts derived from hypertrophic scar tissue or keloid tissue [126].

SLPI also plays a role in unwounded skin. SLPI inhibits shedding from the upper epidermis by inhibiting the keratinocyte product kallikrein-related peptidase 7 (KLK7), which cleaves desmosomes in the stratum corneum [127,128]. SLPI is the major endogenous inhibitor of human KLK7 [128]. Indeed, overexpression of SLPI in the skin results in thickening of the stratum corneum in mice [129,130].

The function of SLPI in skin diseases is not well-studied. SLPI expression is elevated in the lesioned epidermis of patients with psoriasis [131], possibly due to increased production of the growth factors IGF-1 and TGF-α [122,132]. Interestingly, SLPI colocalizes with neutrophil elastase as a component of NETs in psoriatic skin [133]. SLPI, together with neutrophil elastase and DNA, stimulates type I IFN production by plasmacytoid DCs [133], which play a key role in the pathogenesis of psoriasis [134].

In summary, SLPI is essential for murine wound healing, partly by suppressing immune cell infiltration [123]. Whether SLPI also plays a role in human wound healing is unknown, though the increased expression of the protein in keratinocytes in skin wounds suggests SLPI may be involved in wound healing in humans. In addition, SLPI

regulates shedding of the human and murine epidermis [128]. SLPI may also contribute to the development of psoriasis in humans [133]. However, the role of SLPI in chronic skin diseases is largely unknown.

2.3. SLPI in the gastrointestinal tract

SLPI is expressed by epithelial cells in the healthy intestine, in both the Paneth cells at the base of the crypts and goblet cells scattered throughout the epithelium [1]. SLPI expression is induced in intestinal epithelial cells by microbial contact, as colonization of germ-free mice results in colonic SLPI expression [33]. Secretion of SLPI by intestinal epithelial cells, mainly from the apical side, is stimulated by TNF-α, IL-1β and the protein kinase C pathway [37]. SLPI protein levels in intestinal lavage fluid vary widely among healthy individuals [37]. SLPI in intestinal fluid is likely to be locally produced, as salivary SLPI is rapidly degraded in the stomach and duodenum [37,135]. As the concentration of SLPI in luminal fluid is relatively low, the SLPI secreted by epithelial cells is likely to exert its effects locally in the crypt or at the surface of the epithelium [37]. In mice, SLPI protein is expressed at higher levels in the colonic epithelium compared to the small intestinal epithelium [33]. In contrast, higher SLPI protein expression is observed in the lamina propria cells of the small intestine than those of the colon [33]. It is not known whether the higher expression of SLPI in the colonic epithelium is the result of more frequent contact between bacteria and epithelial cells in the colon or due to contact with certain colonic bacteria. SLPI expression increases in the colonic epithelial cells of wildtype mice during induction of acute murine colitis by dextran sodium sulphate (DSS) [136,137]. Oral delivery of lactic acid bacteria expressing murine SLPI or human Elafin ameliorates DSS-colitis in wildtype mice [138]. In thymic stromal lymphopoietin (TSLP)-deficient mice, SLPI expression decreases during DSS-induced colitis [136]. Interestingly, these mice fail to recover from DSS-induced colitis, due to excessive colonic neutrophil elastase activity. Administration of recombinant SLPI reduces the mortality rate of mice with DSS-induced colitis, suggesting that SLPI reduces protease-induced injury in the inflamed intestine [136]. Indeed, SLPI protects intestinal epithelial cells against destruction by neutrophil elastase and trypsin *in vitro* [37]. These findings lead to the question of whether SLPI protects against protease-induced tissue damage in inflammatory bowel disease (IBD). The levels of both neutrophil elastase and SLPI are increased in the intestine of patients with IBD, though it is unclear whether these elevated SLPI concentrations are sufficient to protect against the increased elastase activity [139].

Concomitantly, SLPI plays an anti-inflammatory role during intestinal immune responses. SLPI inhibits NF-κB signaling in intestinal epithelial cells to reduce epithelial chemokine production in response to microbial triggers, and thus prevents continuous leukocyte infiltration at densely colonized mucosal surfaces [33]. This mechanism is acquired directly after birth in the human buccal epithelium, when repetitive microbial interactions induce SLPI and impose acquired hyporesponsiveness within the epithelial cells to microbial signals from the oral microbiota [33]. Similarly, SLPI ensures that the mucosal immune system maintains an adaptive tolerogenic response to harmless protein antigens, despite barrier sites being continually challenged with microbial products. Selective expression of SLPI in the DCs in mucosa-draining lymph nodes locally attenuates DC activation, in particular IL12p70 production, in response to LPS [32]. Thus, SLPI maintains the regulatory T cell response to mucosally encountered harmless proteins [32]. Indeed, *Slpi* knockout mice fail to acquire regulatory T cell-mediated mucosal tolerance to nasal administration of ovalbumin in the presence of low-dose LPS, while tolerance is unaffected in wildtype mice [32,140].

Overall, SLPI protects intestinal tissues from degradation by proteases and against excessive inflammation by attenuating the sensitivity of both intestinal epithelial cells and DCs in mucosa-draining lymph nodes to microbial triggers [32,33]. SLPI is able to kill the intestinal pathogen *Salmonella typhimurium* [37], though the possibility that SLPI shapes the intestinal microbial composition has not been explored. SLPI promotes tissue repair in the oral mucosa via mechanisms similar to those found in the skin [141]. However, it is unknown whether SLPI also contributes to healing of the intestinal mucosa.

Notably, *Slpi* knockout mice do not develop spontaneous intestinal inflammation under SPF conditions [73]. We anticipate that *Slpi* knockout mice may develop intestinal disease after colonization with *Helicobacter hepaticus*, a bacterium that induces colitis in mice with immune regulation defects. In addition, we hypothesize that *Slpi* knockout mice may be more sensitive to infection with *Citrobacter rodentium*, a pathogen that models human infection with *Escherichia coli*. Another notable observation is that decreased SLPI expression does not result in impaired neutrophil infiltration during DSS-induced colitis [136], suggesting that SLPI may not play an essential role in granulopoiesis in mice.

2.4. SLPI in the genitourinary tract

SLPI is expressed by epithelial cells in the female genitourinary tract and secreted into vaginal fluid and cervical mucus [60,142–144]. SLPI is also expressed in epithelial cells in the prostate, seminal vesicles and epididymis and is secreted in seminal plasma [145]. However, the function of SLPI in the male genitourinary tract is unknown.

The antimicrobial capacity of SLPI in the female genitourinary tract has been studied. Perinatal HIV-1 transmission rates are lower among woman with high levels of SLPI in vaginal fluid [143], but whether this effect is due to SLPI inhibiting HIV-1 entering host cells has not been formally demonstrated. The levels of SLPI in vaginal fluid are decreased in women with *Trichomonas vaginalis*, *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infections of the lower genital tract [146]. Moreover, low levels of SLPI in vaginal swab specimens from healthy women have been associated with a higher *Trichomonas vaginalis* load, high vaginal pH and vaginal leukocytosis [147]. These findings suggest either down-regulation of SLPI by these bacteria or pre-existing low levels of SLPI impair bacterial cell killing. Indeed, SLPI exerts bactericidal activity against *Neisseria gonorrhoeae,* and expression of SLPI by reproductive tract epithelial cells *in vitro* is not altered by infection with *Neisseria gonorrhoeae* [144]. However, SLPI can be inactivated by cysteine proteases produced by *Trichomonas vaginalis* [46]. In contrast, *Chlamydia trachomatis* upregulates production of SLPI in cervical epithelial cells [148]. In conclusion, these data indicate a role for SLPI in antimicrobial defense in vaginal fluid. However, establishment of a lower genital tract infection may lead to lower SLPI levels.

2.5. Comparison of the function of SLPI at different barrier sites

SLPI is produced and secreted at barriers by epithelial cells and infiltrating immune cells, such as neutrophils and monocytes. SLPI is upregulated by TLR ligands and pro-inflammatory cytokines in both intestinal and lung epithelial cells. In the respiratory tract, SLPI is an important inhibitor of proteases, and is inactivated in chronic lung diseases characterized by high protease activity. Local administration of recombinant SLPI holds promise for the treatment of chronic lung diseases characterized by excessive protease production. In the gastrointestinal tract, SLPI may also protect tissues from protease-induced damage during inflammation, though this has not been formally demonstrated. Importantly, SLPI regulates epithelial responsiveness to microbial signals in the oral and intestinal mucosa. Whether these mechanisms also occur in respiratory and genital epithelial cells has not yet been explored. In the skin and oral mucosa, SLPI promotes tissue repair after wounding, by both inhibiting proteases and exerting anti-inflammatory activity. Finally, SLPI possesses broad antimicrobial activity; however, the relevance of this function has so far only been established in HIV-1 transmission.

In conclusion, the varied functions of SLPI have not been systematically studied in all tissues (see Table 1 and Fig. 1). Therefore, it remains

Box 3
Mechanisms by which SLPI may influence tumor growth and metastasis

Mechanisms that may prevent cancer:

- Inhibits proteases, resulting in reduced ECM degradation and decreased cell invasion [162,178]
- Induces apoptosis, by inhibiting NF-κB [164] or downregulating E-cadherin and relocating β-catenin [153,169]
- Prevents virus-induced cancers, such as HPV-induced squamous cancer [171,172] and EBV-induced nasopharyngeal carcinoma [174]
- Prevents liver metastases by inhibiting expression of TNF-α and vascular adhesion receptor E-selectin in the liver [179]

Possible cancer-promoting mechanisms:

- Vascular mimicry: promotes formation of vessel-like structures by tumor cells [150]
- Anticoagulative activity [150]
- Promotes cell invasion via induction of MMP-2 and MMP-9 [149,162,169,182]
- Protects the epithelial growth factor progranulin by preventing elastase-mediated degradation or acting as a survival chaperone [159,160,188]
- Promotes cell invasion by reducing production of the antiangiogenic factor Endostatin via inhibiting elastase [178]
- Inhibits apoptosis by inducing cyclin D1 [191]

unclear whether SLPI exerts a unique role in each tissue type, or whether the inflammatory process determines the function of SLPI in specific tissues. We anticipate that SLPI exerts crucial immune regulatory functions in the respiratory tract and genitourinary tract, as in the gastrointestinal tract. In addition, SLPI may promote mucosal wound healing in other barrier tissues comparable to its role in cutaneous wound healing. Further studies of the diverse functions of SLPI in individual tissues will provide a more complete understanding of the roles of this pleiotropic protein in mucosal barriers and the skin.

3. SLPI in cancer

SLPI is upregulated in several types of carcinoma, though its role in cancer has not been completely elucidated. SLPI has been suggested to be involved in cancer via multiple mechanisms (see Box 3). Protease inhibitors were initially anticipated to protect against cancer, as degradation of the ECM is necessary for tumor growth and invasion. However, recent studies showed that SLPI contributes to tumor growth and metastasis; though, counterintuitively, some functions of SLPI may actually protect against cancer.

3.1. SLPI in breast cancer

High *SLPI* mRNA expression correlates with shorter overall survival and shorter distant metastasis-free survival in patients with triple-negative breast cancer [149]. Moreover, in patients with aggressive subtypes of breast cancer, *SLPI mRNA* is expressed at higher levels in the primary tumors of patients with lung metastases than patients without metastases [150].

Importantly, SLPI has been shown to be a driver of metastasis in a mouse model of breast cancer heterogeneity [150]; in this model, orthotopically injected mouse breast cancer clones expressing *Slpi* enter the vasculature more efficiently [150]. SLPI is thought to participate in intravasation, as the metastatic potential was abrogated when the *Slpi* clones were administered via intracardiac injection. Two mechanisms have been proposed to explain the metastasis-promoting role of SLPI. First, SLPI programs tumor cells for vascular mimicry, a process in which tumor cells differentiate into CD31-negative endothelial-like cells and form tubular structures that carry blood to the hypoxic regions of the tumor [150]. Secondly, the metastatic potential of SLPI is reduced in warfarin-treated mice, suggesting that the anticoagulant function of SLPI contributes to its pro-metastatic role [150].

Other researchers also found a metastasis-promoting role for SLPI in mouse models of mammary carcinoma, and several mechanisms have been suggested to explain this observation [149,151]. SLPI interacts with the retinoblastoma tumor suppressor protein, which results in increased translation of target genes such as *MMP2* and *MMP9* [149]. In addition, another study found well-developed sinusoidal vessels surrounded tumor cells overexpressing *Slpi;* the authors suggested that SLPI acts via an invasion-independent metastasis pathway, in which tumor nests enveloped by sinusoidal vessels are released in the bloodstream [151].

In contrast, SLPI induces apoptosis in breast cancer cells *in vitro*, possibly by downregulating E-cadherin to lead to nuclear localization of β-catenin [152,153]. Another study reported that SLPI reduces the growth of murine breast cancer tumors *in vivo* [152].

In summary, multiple studies have shown that SLPI promotes metastasis in mouse models of mammary carcinoma, though the precise mechanisms remain unclear.

3.2. SLPI in ovarian cancer

SLPI expression is increased in ovarian cancer compared to normal ovaries [154,155]. In addition, serum SLPI levels are elevated in patients with early and late stage epithelial ovarian cancer, and serum SLPI can discriminate between patients with malignant and benign ovarian tumors [156–158].

Multiple studies suggest SLPI exerts a pro-metastatic role in ovarian cancer. SLPI promotes proliferation and prevents apoptosis in human ovarian cancer cell lines *in vitro*, independent of its protease inhibitory activity [159,160]. In contrast, other researchers reported that SLPI inhibits cell proliferation, increases apoptosis and decreases the invasive ability of human ovarian cancer cell lines *in vitro* [161]. However, in an orthotopic mouse model of ovarian cancer, overexpression of SLPI led to more metastases, again independent of the protease inhibition activity of SLPI [159,162].

One possible mechanism that may explain the tumor-promoting effects of SLPI is its ability to protect the survival factor progranulin, partly via inhibition of elastase-induced degradation [160] or independently of protease inhibition [159]. Another possibility is that SLPI increases MMP-9 production, independently of its protease inhibitory function [162]. Overall, the evidence indicates SLPI is upregulated in ovarian cancer and acts as a pro-tumorigenic factor in mouse models, possibly by protecting progranulin and inducing MMP-9.

3.3. SLPI in squamous cell carcinoma of the head and neck (HNSCC)

In contrast to most other carcinomas, SLPI is expressed at low levels in HNSCC. SLPI is downregulated in oral premalignant lesions and oral squamous cell cancer compared to normal oral epithelium [163,164]. In addition, high SLPI expression in oral premalignant lesions was associated with lower histological grade [165]. Surprisingly, expression of SLPI in oral squamous cell carcinoma is associated with a better prognosis [166]. Moreover, SLPI is expressed at higher levels in the HNSCC tumors of patients without lymph node metastases compared to patients with lymph node metastases [167]. In contrast, expression of SLPI in tonsillar squamous cell carcinoma is associated with shorter overall survival [168].

SLPI is thought to play a role in HNSCC via multiple mechanisms, which makes it difficult to dissect the net effect of SLPI. Some *in vitro* studies have suggested that SLPI reduces migration, invasion and proliferation and induces apoptosis in human HNSCC cells [163,165]. In contrast, other studies found that knockdown of *SLPI* decreased the migration, invasion and proliferation of oral carcinoma cells [169,170]. *MMP2* and *MMP9* mRNA expression are downregulated in *SLPI*-knockdown oral carcinoma cells, suggesting that SLPI promotes invasion by inducing MMPs [169].

The antiviral activity of SLPI may also be relevant in HNSCC. SLPI can prevent human papillomavirus 16 (HPV16) infection by blocking the epithelial receptor annexin A2, which suggests SLPI could prevent HPV-induced HNSCC [171]. Indeed, SLPI is expressed at lower levels in HPV-positive HNSCC than HPV-negative HNSCC [172,173]. In addition, SLPI may prevent Epstein-Barr virus (EBV) infection, as SLPI expression is associated with an absence of EBV in nasopharyngeal carcinoma [174]. However, the precise role of the antiviral activity of SLPI in the development of HNSCC has not been defined.

Finally, SLPI can inhibit NF-κB signaling in oral premalignant cells *in vitro* [164,165]. Activation of NF-κB signaling is associated with the progression from oral premalignant cells to oral squamous cell cancer [164,165]; however, whether SLPI actually prevents the progression to HNSCC is unknown.

In conclusion, SLPI is downregulated in HNSCC and may exert both effects protective against cancer—such as antiviral activity and inhibition of NF-κB—as well as cancer-promoting effects, such as stimulating cell invasion.

3.4. SLPI in lung cancer

SLPI is expressed in adenocarcinoma and squamous cell carcinoma of the lung (non-small cell lung cancer, NSCLC) at higher levels than in small cell lung cancer [175]. Patients with NSCLC also have higher serum SLPI levels compared to healthy controls [175]. Moreover, patients with stage III or IV NSCLC have higher serum SLPI levels than patients with stage I or II NSCLC and serum SLPI decreases after treatment [175], suggesting a relationship between serum SLPI and tumor size or progression. However, the precise function of SLPI in lung carcinoma is unclear.

SLPI stimulates the proliferation of human lung adenocarcinoma cell lines *in vitro* [176]. However, other researchers reported SLPI did not affect proliferation or TNF-α-mediated apoptosis in murine lung carcinoma cells [177,178]. Transfection of human *SLPI* enhanced subcutaneous tumor growth and the lung-colonizing potential of murine lung carcinoma cells that were intravenously injected into immunocompromised mice [178]. Mutant SLPI with lower protease inhibitory capacity did not increase tumor growth and lung-colonizing potential in the same model, suggesting the cancer-promoting mechanism of SLPI is dependent on its protease inhibitory function [178]. In contrast, overexpression of SLPI in a liver-metastatic subclone of the same cell line resulted in fewer liver metastases after intrasplenic injection [179]. SLPI blocked the induction of *Tnf* mRNA expression in the liver in response to tumor cell infiltration, and this effect was thought to be tumor-promoting in this model [179].

In conclusion, the evidence indicates SLPI is upregulated in NSCLC and may act as a tumor-promoting factor in lung cancer.

3.5. SLPI in gastric cancer

SLPI is overexpressed and associated with shorter five-year survival in gastric carcinoma [180,181]. *In vitro*, SLPI promotes the migration, invasion and proliferation of human gastric cancer cells [180–182]. SLPI upregulates MMP-2 and MMP-9 protein expression via phosphorylation of Elk-1 in gastric cancer cells, which could explain the enhanced invasive ability of SLPI-expressing gastric cancer cells [182]. Whether SLPI promotes metastasis in gastric cancer remains to be investigated.

3.6. SLPI in colorectal cancer

The role of SLPI in colorectal cancer is largely unknown. A highly metastatic human colorectal cancer cell line was found to secret increased levels of SLPI compared to the poorly metastatic parental line [149]. Additionally, SLPI is expressed in a subgroup of human colorectal carcinomas [183]. High SLPI protein expression in colorectal cancer liver metastases was associated with shorter overall survival after resection of the liver metastases [184]. In addition, mice subcutaneously injected with SLPI-overexpressing murine colon cancer cells developed tumors more rapidly than mice injected with control cells [152]. Therefore, SLPI may play a role in colorectal cancer metastases. However, the exact role of SLPI in human colorectal cancer remains to be elucidated.

3.7. SLPI in pancreatic cancer

SLPI protein expression is upregulated in human pancreatic carcinoma compared to peritumoral tissue [185]. Moreover, knockdown of *SLPI* reduced proliferation, migration and invasion and increased apoptosis in human pancreatic cancer cells *in vitro* [185,186]. However, *in vivo* studies are needed to reveal whether SLPI promotes tumor growth and metastasis in pancreatic cancer.

3.8. SLPI in prostate cancer

SLPI expression is decreased in prostate carcinoma compared to normal prostate tissue and benign prostatic hyperplasia [187]. However, *SLPI* mRNA expression is upregulated in prostate cancer metastases compared to primary tumors, and patients with metastatic prostate cancer have higher serum SLPI levels than patients with localized disease [188]. In addition, knockdown of *SLPI* reduced castration-resistant prostate cancer cell proliferation and invasion and increased apoptosis *in vitro* [188]. Moreover, overexpression of *SLPI* in human prostate cancer cells led to formation of larger tumors after subcutaneous injection in immunocompromised mice; this tumor-promoting effect was suggested to be due to the ability of SLPI to protect progranulin and confer resistance to TNF-α-induced apoptosis [188]. In conclusion, SLPI is low in primary prostate cancer but upregulated in metastases, and SLPI may promote prostate cancer growth and metastasis.

3.9. SLPI in other types of cancer

SLPI protein expression is decreased in cervical adenocarcinoma compared to normal endocervical glands, and was not associated with patient survival [189]. In vulvar squamous cell cancer *SLPI* mRNA expression is associated with HPV-negative carcinomas [190]. SLPI has been shown to promote the proliferation of human endometrial adenocarcinoma cells, possibly by inducing Cyclin D1 [191]. Moreover, patients with papillary thyroid cancer have higher serum SLPI levels than healthy controls or patients with multinodular nontoxic goiter [192].

Table 2
Function of SLPI in various carcinomas based on human and animal studies.

	Prevention of tumor growth or metastasis	Promotion of tumor growth or metastasis
Breast cancer	• Induces apoptosis (*in vitro*) [152,153] • Inhibits tumor growth (*in vivo*) [152]	• Promotes metastasis (*in vivo*) [149,150,151]
Ovarian cancer	• Inhibits cell growth and invasion, and promotes apoptosis (*in vitro*) [161]	• Promotes proliferation and prevents apoptosis (*in vitro*) [159,160] • Promotes tumor growth and metastasis (*in vivo*) [159, 162]
HNSCC	• Inhibits cell migration, invasion and proliferation; induces apoptosis (*in vitro*) [163,165]	• Promotes migration, invasion and proliferation (*in vitro*) [169,170]
Lung cancer	• Prevents liver metastasis (*in vivo*) [179]	• Stimulates proliferation (*in vitro*) [176] • Promotes tumor growth (*in vivo*) [178]
Gastric cancer	• Unknown	• Promotes migration, invasion and proliferation (*in vitro*) [180,181,182]
Colorectal cancer	• Unknown	• Promotes tumor development (*in vivo*) [152]
Pancreatic cancer	• Unknown	• Promotes proliferation, migration and invasion; prevents apoptosis (*in vitro*) [185,186]
Prostate cancer	• Unknown	• Promotes proliferation, invasion and prevents apoptosis (*in vitro*) [188] • Promotes tumor growth (*in vivo*) [188]
Endometrial cancer	• Unknown	• Promotes proliferation (*in vitro*) [191]

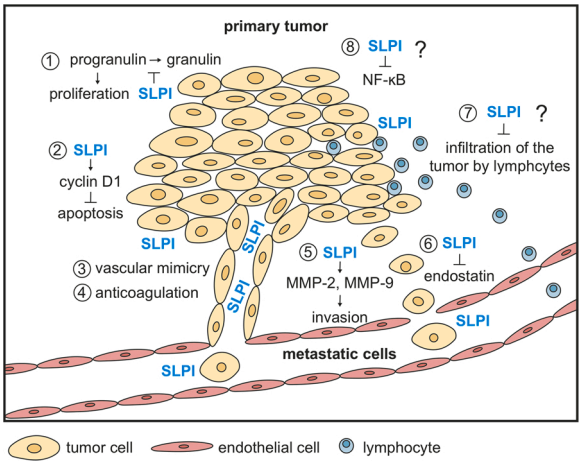

Fig. 2. Mechanisms by which SLPI may promote cancer.
Production of SLPI by epithelial tumor cells may promote cancer via several mechanisms. (1) SLPI prevents conversion of the epithelial growth factor progranulin to granulin. (2) SLPI promotes cell proliferation by inducing cyclin D1. (3) SLPI induces the formation of vessel-like structures (vascular mimicry), which provide a blood supply to hypoxic regions of the tumor. (4) SLPI acts as an anticoagulant. (5) SLPI promotes tumor cell invasion by inducing MMP-2 and MMP-9 production by tumor cells. (6) SLPI inhibits the antiangiogenic factor Endostatin. (7) We hypothesize that SLPI prevents infiltration of lymphocytes into the tumor. (8) Whether SLPI inhibits activation of NF-κB in tumor cells is unclear.

3.10. Conclusions

SLPI is upregulated in several types of carcinoma. In addition, SLPI is expressed at higher levels in many metastatic cell lines compared to their poorly metastatic counterparts, suggesting SLPI plays a role in metastasis [149,179,182,193,194]. While the function of SLPI in cancer is yet not entirely clear, most studies indicate SLPI promotes metastasis (see Table 2 and Fig. 2). Some of the *in vitro* and *in vivo* findings on the effect of SLPI on cell proliferation, migration and invasion conflict, possibly due to the complex interactions between SLPI and the factors produced by cells in the tumor microenvironment *in vivo*. SLPI is likely to exert multiple functions at different stages of tumor development and progression, which may not all be cancer-promoting.

In addition, the *in vivo* effects of SLPI in cancer have mostly been studied by injecting human cancer cells into immunocompromised mice [150,159,178,188]. Therefore, the possible role of SLPI in anti-cancer immune responses is an important knowledge gap. In view of its strong anti-inflammatory functions in healthy mucosa, SLPI is likely to suppress anti-tumor immune responses as well. We suggest this hypothesis should be tested by examining the associations between SLPI expression in carcinomas and the presence and activity of tumor-infiltrating immune cells.

Surprisingly, the functions of SLPI in tissue damage and chronic inflammation—such as immune regulation, tissue healing and antimicrobial activity—have not yet been studied in cancer. Tumor SLPI expression varies between patients, and high tumor SLPI expression has been linked to a poor prognosis in breast cancer and gastric cancer [149, 150,180,181]. Therefore, additional study of the role of SLPI in tissue damage and chronic inflammation in different types of cancer is likely to reveal the mechanisms by which SLPI promotes cancer. Finally, the possible link between increased SLPI expression during chronic inflammation and increased SLPI expression in cancer remains to be explored.

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CRediT authorship contribution statement

Sandrine Nugteren: Conceptualization, Investigation, Writing - original draft, Visualization. **Janneke N. Samsom:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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