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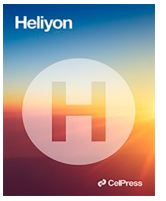

Review article

The secretory leukocyte protease inhibitor (SLPI) in pathophysiology of non-communicable diseases: Evidence from experimental studies to clinical applications

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A B S T R A C T

Non-communicable diseases (NCDs) are a worldwide health issue because of their prevalence, negative impacts on human welfare, and economic costs. Protease enzymes play important roles in viral and NCD diseases. Slowing disease progression by inhibiting proteases using small-molecule inhibitors or endogenous inhibitory peptides appears to be crucial.

Secretory leukocyte protease inhibitor (SLPI), an inflammatory serine protease inhibitor, maintains protease/antiprotease balance. SLPI is produced by host defense effector cells during inflammation to prevent proteolytic enzyme-induced tissue damage. The etiology of noncommunicable illnesses is linked to SLPI's immunomodulatory and tissue regeneration roles. Disease phases are associated with SLPI levels and activity changes in regional tissue and circulation. SLPI has been extensively evaluated in inflammation, but rarely in NCDs. Unfortunately, the thorough evaluation of SLPI's pathophysiological functions in NCDs in multiple research models has not been published elsewhere. In this review, data from PubMed from 2014 to 2023 was collected, analysed, and categorized into *in vitro*, *in vivo*, and clinical studies.

According to the review, serine protease inhibitor (SLPI) activity control is linked to non-communicable diseases (NCDs) and other illnesses. Overexpression of the SLPI gene and protein may be a viable diagnostic and therapeutic target for non-communicable diseases (NCDs). SLPI is also cytoprotective, making it a unique treatment. These findings suggest that future research should focus on these pathways using advanced methods, reliable biomarkers, and therapy approaches to assess susceptibility and illness progression. Implications from this review will help pave the way for a new therapeutic target and diagnosis marker for non-communicable diseases.

1. Introduction

Noncommunicable diseases (NCDs), also referred to as chronic diseases, have prolonged durations and arise from a complex interplay of genetic, physiological, environmental, and behavioral determinants. The main categories of NCDs encompass cardiovascular disorders, including heart attacks and strokes, malignancies, chronic respiratory diseases, such as chronic obstructive pulmonary disease and asthma, as well as diabetes [1]. NCDs contribute to the mortality of approximately 41 million individuals annually,

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constituting around 74% of the total worldwide fatalities. Almost 77 % of fatalities caused by NCDs are found in countries with low- and middle-income economies [1]. The identification, assessment, and management of NCDs, together with the provision of palliative care, are fundamental elements in addressing the challenges posed by NCDs. The 2030 Agenda for Sustainable Development acknowledges that non-communicable diseases (NCDs) pose a significant obstacle to achieving sustainable development [1,2].

Proteases, referred to as proteolytic enzymes or proteinases, are a category of enzymes that play a vital role in the process of protein hydrolysis by breaking peptide bonds. Numerous proteases have been found to exert significant functions in the context of inflammation, including matrix metalloproteinases (MMPs), neutrophil elastase (NE), serine proteases, cathepsins, caspases, and kallikreins [3,4]. The regulation of inflammatory proteases, particularly by endogenous anti-protease molecules, is crucial for sustaining controlled, targeted inflammation and serves to ensure that the inflammatory response is adequately constrained and confined to the necessary extent. Nevertheless, in circumstances where the regulation of these proteases is compromised or in conditions of chronic inflammation, the induction of tissue damage will be unable to be controlled and consequently contribute to the emergence of non-communicable diseases (NCDs).

Secretory leukocyte protease inhibitor (SLPI), a ~12 kDa nonglycosylated cationic protein, was initially characterized for its role as a serine protease inhibitor. A subsequent study has further elucidated that the involvement of SLPI in the inflammatory response is among the several reactions triggered by pathogenic infections [5]. The number of scholarly articles discussing the functions, impacts, processes, and potential use of SLPI as biomarkers in non-communicable diseases (NCDs), such as neurodegenerative diseases, respiratory disorders, urology, obstetrics and gynaecology disorders, liver diseases, kidney diseases, ocular diseases, bone, cartilage, and dental disorders, metabolic diseases, cancer, and cardiovascular diseases, has been increasing, particularly in recent decades. The objective of this review is to provide a comprehensive overview and analysis of the available information derived from *in vitro*, *in vivo*, and clinical investigations regarding the functions, effects, mechanisms, and possible applications of SLPI as biomarkers. The fundamental processes associated with SLPI activity are also being explored. The data derived from this analysis include valuable information on the potential of SLPI as a new therapeutic agent or biomarker for non-communicable diseases (NCDs).

2. Literature review methodology

Ten-year publications from 2013 to 2023 were collected from MEDLINE (via PubMed). The search terms were “SLPI”, “ALP”, “MPI”, and “ALK1”. The search criteria were original research articles published in English. 76 articles were found to be relevant (30 *in vitro* studies, 18 *in vivo* studies, and 28 clinical studies) with 2 brain and spinal cord injuries, 10 respiratory disorders, 8 urology, obstetrics, and gynaecology disorders, 2 liver disease, 8 kidney disease, 2 ocular disease, 5 bone, cartilage, and dental disorders, 29 cancer, and 10 cardiovascular diseases included in this review.

3. The biological and biochemical properties of SLPI

3.1. Structure of SLPI

The secretory leukocyte protease inhibitor (SLPI) is a non-glycosylate protein [6] with an 11.7 kDa boomerang-like shape (Fig. 1a) that contains two whey acidic protein (WAP) domains connected by four disulfide linkages [7,8] (Fig. 1b). The WAP II or *C*-terminal domain of the SLPI has been implicated in protease inhibitory action [9], which specifically targets serine protease enzymes. The protease inhibitory domain resides at residues 67–74 [9], and in particular, Leu72-Met73-Leu74 are crucial for the antiprotease activity (Fig. 1b and c) [10]. Although it has been known that the protease inhibitory activity of SLPI is independent of WAP domain I, or *N*-terminal domain. WAP domain I possesses a variety of beneficial biological effects. It is essential for broad-spectrum antimicrobial activity [11–13]. SLPI can directly kill bacteria and fungi [11–14] and also interfere with the human immunodeficiency virus 1 (HIV-1) infection in macrophages by competitively binding to annexin II or scramblase 1 and 4 [15,16], which is considered a binding partner protein for SLPI and involved in the intracellular transport of SLPI protein [17]. Therefore, *N*-terminal domain or WAP domain I, although it does not implicate anti-protease activity, but it plays important roles in biological function.

3.2. SLPI substrates

Inflammatory serine proteases are substrates of SLPI. One of the most abundant protease enzymes is neutrophil elastase (NE), in which the inhibition of neutrophil elastase requires the association between SLPI and fibronectin or elastin by tissue transglutaminase-2 and plasma factor XIIIa [18]. Although SLPI has been known to inhibit NE activity, NE itself could regulate SLPI expression [19]. Moreover, SLPI can inhibit cathepsin G, chymase, chymotrypsin, trypsin, and tryptase activity [20–23], and is known to inhibit the production and activity of matrix metalloproteinases (MMPs) [24]. The inhibition of plasmin by SLPI blocks the plasminogen activator through Annexin A2 leading to reduced plasmin generation [25]. Although SLPI can inhibit the protease activity, but the protease can also inactivate the SLPI itself. Secreted SLPI can be inactivated by myeloperoxidase-catalysed oxidation from activated neutrophils [26]. Previous studies reported that SLPI could be digested by matrix metalloprotease-9 (MMP-9), which subsequently suppresses the protease inhibitory activity of SLPI [27]. Furthermore, cleaved-SLPI loses its ability to inhibit monocyte MMP-9 synthesis, implying that excessive MMP-9 production can overcome SLPI [14,27]. Similar to the case of MMP-9, chymase is also known to cleave and suppress the protease inhibitory activity of SLPI [20,28]. SLPI can also be digested by cathepsins B, L, and S, which renders their anti-neutrophil elastase function inactive [20]. This also causes a reduction of the half-life in circulation [29].

3.3. Regulation of SLPI expression

Human SLPI protein was encoded from the region of 678 kb on chromosome 20q12–13.2 [8]. SLPI has been shown to be expressed in a variety of cells, including human epithelial cells, immunological cells, and fibroblasts [30–32]. A high concentration of SLPI is secreted in saliva and mucosal tissues. The concentration of SLPI in the saliva is 30 times higher than in the circulation [33]. Regulation of SLPI mRNA expression is upregulated by several stimulants/activators (Fig. 2a) such as pattern recognition receptor ligands, including Toll-like receptor (TLR) ligands [14,34,35]. Therefore, microorganisms are able to induce SLPI expression from their cell components, including lipopolysaccharide (LPS) of a bacterial cell wall, viral RNA, and parasites [36–39]. In addition, SLPI expression in epithelial cells can be stimulated by several types of cytokines including tumour necrotic factor (TNF), interleukin-1 beta (IL-1 β), transforming growth factor alpha (TGF-α), insulin-like growth factor 1 (IGF-1), progesterone, and corticosteroids [40–42]. In macrophages, interferon (IFN) and IL-10 have been shown to upregulate SLPI expression, while IL-6 was found to downregulate the expression of SLPI [43,44]. Interestingly, IFN-γ can reduce TNF-α and nitric oxide (NO) production in macrophages to tolerance to SLPI [34,45]. This information suggested that pro-inflammatory cytokines and cell components regulate SLPI expression. Moreover, SLPI gene expression can also be regulated in response to external physiological, chemical, and biological stimulant including estrogenic [46], endothelial growth factor (EGF) [47,48], sulforaphane, cruciferous vegetables, via activation of Nrf2 [49], parathyroid hormone (PTH) [50], progesterone [51] and corticosteroids [52] (Fig. 2a).

Although the fact that the anti-inflammatory action of SLPI against inflammatory proteases has been extensively published and analysed in various review publications, information on the effect of SLPI, particularly in non-communicable diseases (NCDs), has never been studied elsewhere. In this review article, we compiled data from the last decade on the role and impact of SLPI in NCDs like brain and spinal cord injury, SLPI in respiratory disorders, urology, obstetrics, and gynaecology, liver diseases, kidney diseases, ocular diseases, bone, cartilage, and dental disorders, cancer, metabolic diseases, and cardiovascular diseases.

SLPI posses several biological activities, which can be partially explained by its intracellular mechanisms, which purpose in Fig. 2b. The inhibition of apoptosis is achieved by SLPI through the suppression of Bax, Cytochrome *c*, caspase 3, and caspase 8. Additionally, it has been observed that it downregulates the expression of p38 MAPK, a protein that is triggered by reactive oxygen species (ROS), while simultaneously upregulating the PI3K pathway, leading to increased expression of Akt. This upregulation of Akt subsequently triggers the synthesis of bcl-2 [53–57]. The stimulation of SLPI results in the upregulation of cyclin D1, hence facilitating cellular proliferation [58]. The anti-inflammatory effects of SLPI are mediated through the inhibition of NF-κB [59], MMP expression [24], and neutrophil elastase (NE) [60]. Additionally, SLPI binds to Annexin A2, therefore safeguarding tissue plasminogen activator (t-PA) from converting to plasmin, which is known to induce MMP activity [61]. The functionality of SLPI ceases [24], leading to its interaction with Annexin A2 in order to safeguard tissue plasminogen activator (t-PA) from undergoing conversion into plasmin, hence preventing the activation of matrix metalloproteinase (MMP) activity [25]. The SLPI protein has the ability to interact with many binding partner proteins, including Annexin A2, Scramblase 1, Scramblase 4, and S100A10. These binding partner proteins play a crucial role in facilitating the intracellular transport of the SLPI protein [17]. The SLPI protein stimulates the production of glutathione, which acts as an antioxidant, through the presence of its cysteine residues [62]. The upregulation of FoxM1 target proteins is induced by SLPI,

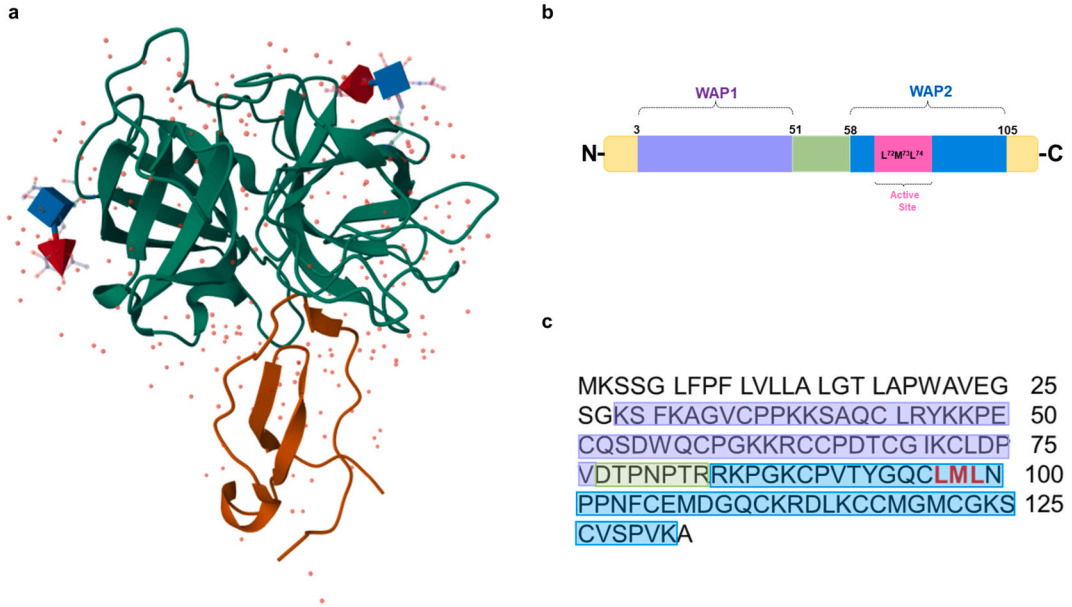

Fig. 1. SLPI structure and biochemical property. (a) Structure of SLPI is boomerang-like shape [223], which contains two whey acidic protein (WAP) domains (b). SLPI compose of 134 amino acids, where Leu72-Met73-Leu74 are crucial for the antiprotease activity (c).(modified from Majchrzak-Gorecka et al., 2016 [5].)

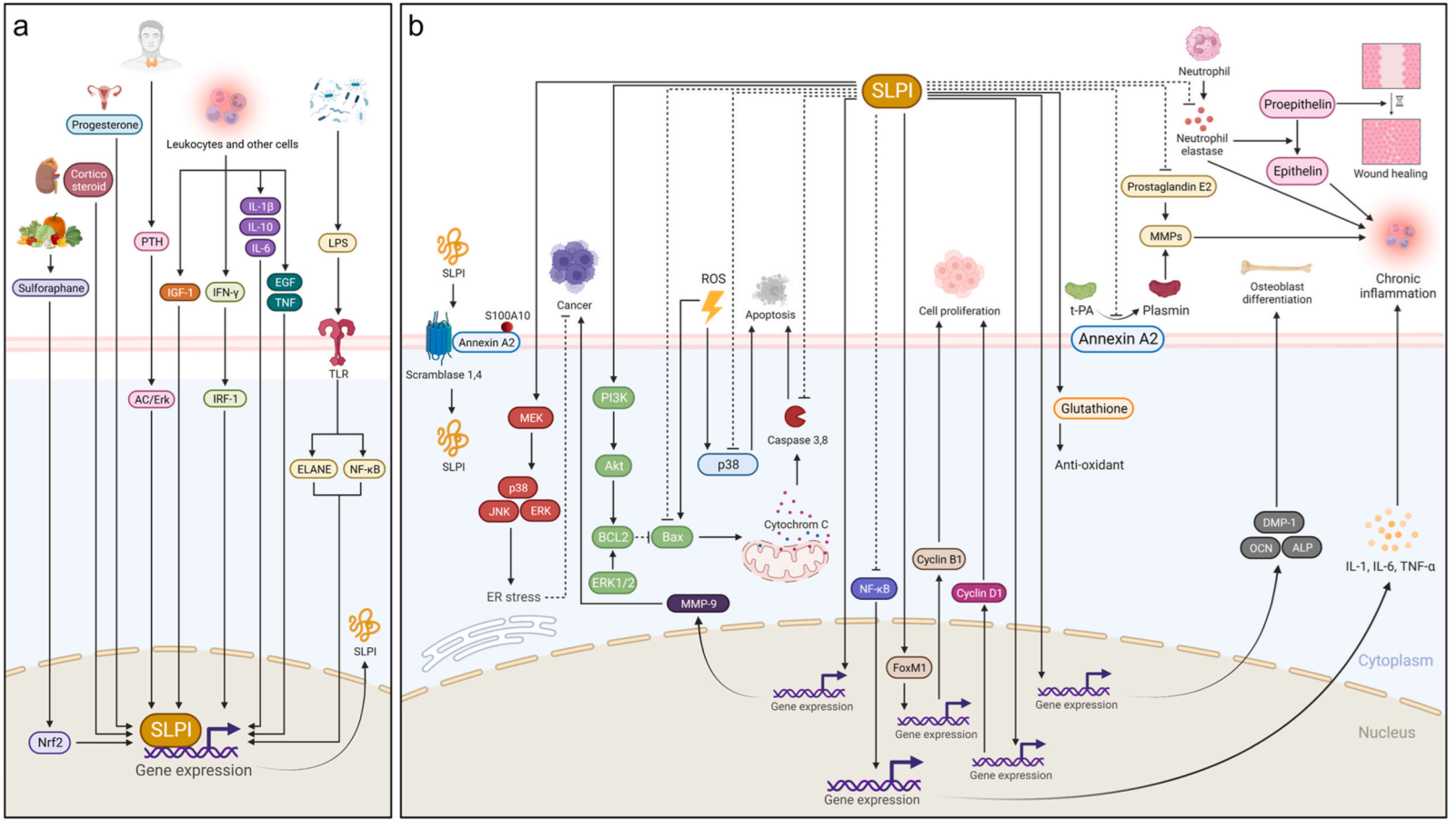

Fig. 2. Schematic diagram on the molecular mechanisms of the regulation of SLPI gene expression (a), and mechanisms of SLPI activity (b).

resulting in the activation of FoxM1 binding to FoxM1 target genes, including cyclin B1, which facilitates cell division [63]. The Stimulation of Localized Protein Interaction (SLPI) has been found to have a positive effect on the viability and specialisation of osteoblasts throughout the process of osteoblastogenesis. Furthermore, it has been observed that SLPI enhances the upregulation of ALP, osteocalcin (OCN), and DMP-1 during the mineralization process of osteoblasts [64]. The upregulation of SLPI has been found to enhance the expression of MMP-9, hence promoting the growth of cancer [65]. Nevertheless, the SLPI compound has been observed to trigger apoptosis in cancer cells by stimulating endoplasmic reticulum stress (ER stress) through the activation of the MEK/ERK pathway [66].

4. Role of SLPI in non-communicable diseases (NCDs)

Although the roles and effects of SLPI have been studied for decades, but a majority of the evidence was highlighted in infectious conditions and immunity against microbial infection, which has been intensively reviewed by several articles [5,67–74]. However, a review of the literature focusing on the roles and effects of SLPI in non-communicable diseases (NCDs), not only the major types of NCDs but also other NCDs is still required. The data presented in this study encompasses findings from *in vitro*, *in vivo*, and *clinical investigations*, as documented in published publications and subsequently synthesised across several organ system models.

4.1. SLPI in regulating cell proliferation, differentiation, and apoptosis

The roles of SLPI in cell proliferation have been well described in the cancer model, in which SLPI promotes cell proliferation through the transcriptional activation of cyclin D1, which is an important regulator of cell cycle progression and activates cell proliferation [5]. In addition to activating cell renewal, the anti-apoptotic activity of SLPI has also been reported. SLPI could inhibit TNF-α-induced apoptosis by downregulating pro-apoptotic caspase-3 [75]. The evidence of SLPI in several types of cancer has been reported and also mentioned in the latter section of this review article.

4.2. SLPI and brain and spinal cord injury

Brain injury can result from several factors, including degenerative processes, as well as stroke or ischemia. Ischemic brain damage can be attributed to many processes, including the inflammatory response and the buildup of substances, both of which have the potential to impact brain function [76]. Nevertheless, accidental damage to neurological organs also has an impact on the functioning of the central nervous system, which encompasses spinal cord injuries. The occurrence of spinal cord injury has shown a progressive increase with advancing age, making it a significant lesion to the central nervous system [77]. Based on a prior investigation, it has been determined that traffic accidents are the predominant factor contributing to spinal cord damage, with a significant proportion of 57.6 % [78]. In Korea, those who have experienced spinal cord injuries are commonly perceived as having a physical handicap and are sometimes grouped together with other types of disabilities [79]. Therefore, the indicators associated with the extent of harm or the proteins that mitigate the processing of injury may possess therapeutic efficacy for these medical conditions.

Secretory leukocyte protease inhibitor (SLPI) is commonly found on mucosal surfaces, including saliva, and in epithelial cells of the respiratory tract and urogenital tract [80,81]. However, SLPI showed a response to central nervous system (CNS) injury, including cerebral ischemia and spinal cord injury [82,83]. In the focal cerebral ischemia model, generated by unilateral middle cerebral artery occlusion (MCAO), the upregulation of SLPI in the ipsilateral cortex by cerebral ischemia at 12–48 hours was observed, and the SLPI level continually increased after 5 days of MCAO [82]. Furthermore, overexpression of SLPI significantly lowered neurological deficit scores [82]. The neuroprotective effect of SLPI was also demonstrated in the traumatic CNS injury model involving a moderate contusion injury at T11. The SLPI mRNA was expressed at 1 day after the injury, whereas the SLPI protein could be observed at 3 days after the injury. In addition, administration of recombinant SLPI significantly improved motor function as assessed by the Basso Mouse Scale (BMS). Moreover, receiving SLPI could increase tissue sparing, myelin integrity, the number of ventral horn neurons, and the density of serotonergic axons caudal to the lesion [83] **(Table 1).**

In summary, the levels of SLPI were shown to be correlated with cerebral ischemia injury in the middle cerebral artery occlusion (MCAO) model as well as spinal cord injury. Additionally, the SLPI treatment exhibited enhanced motor function, as shown by improvements in the Basso Mouse Scale (BMS) and cell population.

4.3. SLPI in respiratory disorders

In a global view, respiratory disorder was also the most common non-communicable disease worldwide due to the noxious environment and behavioral inhalational exposures [84]. The global burden of diseases, injuries, and risk factors study (GBD) 2017 found that around 545 million people in the world had chronic reparatory disease in 2017, which increased 39.8% since 1990, especially chronic obstructive pulmonary disease (COPD), which was the most prevalent, accounting for 3.9% of global prevalence [85]. Interestingly, the various studies of respiratory disorders were due to the increase of protease enzymes in their disease's progression, which could increase inflammation and pathology [86]. Therefore, a potential protein expression that can indicate and alter the effect of inflammation and pathology in respiratory disorders should be beneficial for the patient.

In the respiratory airway, the balance of proteases and anti-proteases could indicate the immune response in inflammatory site, especially in cystic fibrosis (CF). CF cause ineffective innate immunity by transmembrane conductance regulator mutation that impair ion channel and mucociliary clearance [87]. These led to chronic pathogen colonization from *Pseudomonas aeruginosa*, and an

inflammatory response located in both the upper and lower airways as reservoirs of infection, so discrimination of pathogen location leads to therapeutic treatment for specific immune compartments [88]. It has been reported that the level of proteases and anti-proteases by concentration were significantly higher in the sputum of CF patients compared to nasal lavage (NL) from healthy subjects, as were 10-fold neutrophil elastase (NE) and 5000-fold of SLPI. Furthermore, the NE/SLPI ratio in NL was 726-fold higher than that in sputum, respectively [89]. Likewise, for the NL and sputum of CF patients before and after intravenous (IV) antibiotic therapy, IV antibiotic treatment was significantly promoted an inflammatory response in the lower airway, but the trend was decreasing in the upper airway. The MMP9/TIMP1 and NE/SLPI ratios were significantly higher in sputum when compared to NL. In addition, the NE/SLPI ratio was 10-fold higher in NL compared to healthy people. The upper airway was indicated to have delayed anti-protease and protease responses to IV-antibiotic therapy compared to the lower airway. Then, changes in microbiological patterns occurred after treatment with antibiotic therapy that were associated with changes in protease and anti-proteases imbalances [90]. For the protease activity in the animal model, the clinical significance of SLPI has been reported in genetically modified animal models lacking SLPI expression, whereby the bleomycin was used to develop a lung fibrosis model in mice, which found that there was an increase in MMP9 activity in *slpi*$^{-/-}$ mice, which was related to the impairment of collagen gene expression but reduced lung fibrosis. In addition, the protease mediated TGF-β activity increased above their increased in wild-type mice after *slpi*$^{-/-}$ mice were treated with bleomycin that impaired collagen gene expression but there was minimal reduction of lung fibrosis so SLPI knockout could not prevent the development of lung fibrosis following bleomycin-induced lung injuries [91].

The shift between protease and anti-protease balance was not only found in CF, but was also found in chronic obstructive pulmonary disease (COPD) following cigarette smoking. The study of differentiated nasal epithelial cells (NECs) and nasal lavage fluid (NLF) in smokers and non-smokers showed an increase in SLPI levels in NECs and NLF from smokers. The interferon-sensitive response element (ISRE) binding sites were one of the regulatory sites of the SLPI promoter [92]. Transcription factors of the interferon signalling pathway, STAT1, could regulate SLPI expression in the epithelial cells and lungs of *stat1*$^{-/-}$ mice compared to wild-type. This finding showed that SLPI regulation and activity in the nasal mucosa were induced by smoking [93]. Similarly, bronchial epithelial cells show an increase in SLPI production after treatment with TGF-β1 neutralizing antibodies that seems to like its partially restored SLPI production during hypoxia [94].

SLPI was downregulated in both humans and mice with severe asthma (SA) in correlation with poor lung function. This could be due to the upregulation of interferon-gamma (IFN-γ) in the chronic inflammatory model. The IFN-γ attenuates SLPI expression in airway epithelial cells and could indirectly activate protease activity from the mast cells, which contributes to the severity of involvement in increased airway hyperresponsiveness (AHR) in mice [95]. SLPI seems to have therapeutic benefits since overexpression of SLPI could ameliorate AHR and was more efficiently treated when treated in combination with corticosteroids (CS). The effective treatment for severe asthma patients was bronchial thermoplasty (BT), which is an endoscopic therapy that targets the smooth muscle in the lungs [96]. This technique could downregulate several genes that are involved in airway inflammation and remodelling in patients with severe asthma. Interestingly, the results showed that SLPI was observed in patients who had fewer than 2 exacerbations post-BT [97]. Similarly, Ano S. et al. reported that responsive patients showed SLPI gene upregulation, which suggests that SLPI could potentially be useful for identifying the risk of exacerbations post-BT [98] (Table 2).

In summary, SLPI is positively associated with respiratory disorders due to protease enzyme activity and inflammatory response, especially in the patient's sputum in cystic fibrosis. In addition, SLPI could also provide therapeutic potential in combination with corticosteroids in respiratory disorders.

4.4. SLPI in urology, obstetrics and gynaecology disorders

In the final period of the pregnancy, the uterine cervix was changed to soft tissue, which was called cervical remodelling. These

Table 1
SLPI in brain and spinal cord injury.

Species	Study models	Readout	Outcomes	References
Rat	Focal Brain Ischemic rat (middle cerebral artery (MCA) was permanently occluded and cut dorsal to the lateral olfactory tract at the level of the inferior cerebral vein and treated with 1.0×10^{12} particles/ml adenovirus construct Adv/GFP	Northern blot analysis Immunohistochemical and confocal microscopy analysis.	SLPI mRNA was induced in the ischemic brain tissue at 12 h, peaked at 2 days and sustained up to 5 days Administration of a recombinant adenovirus overexpressing SLPI (Adv/SLPI) into the cortical tissue resulted in up to 58.4 % reduction in ischemic lesion over controls at the site of Adv/SLPI expression improved functional outcome	[82]
Mice	Spinal cord injury by partial laminectomy made using Mouse Laminectomy Forceps [Fine Science Tools (FST), Vancouver] at the 11th thoracic vertebral level. SLPI transgenic over-expressing C57BL/6 J mice (endogenous effect) C57BL/6 J mice was injected intraperitoneally with 1 mg recombinant mouse SLPI per gram initial body weight in 200 ml total solution. (exogenous effect)	Real-time PCR Western blot analysis Leukocyte isolation and Immunofluorescence labelling	An increased level of SLPI in the first week after spinal cord injury has beneficial effects in terms of histological outcomes and locomotor function. SLPI in reducing NF-kB activation and TNF-a expression after spinal cord injury.	[83]

Table 2
SLPI in respiratory disorders.

Species	Study models	Readout	Outcomes	References
Mice	slpi−/− mice on a B6D2F1 (oropharyngeal administration of bleomycin (30 IU) and the development of pulmonary fibrosis)	Lung fibrosis was determined by collagen subtype-specific gene expression, hydroxyproline concentration, and histological assessment pSmad2, TGF-B activity by immunohistochemistry.	The active-MMP-9 to pro-MMP-9 ratio was significantly increased in Slpi (−/−) animals Slpi (−/−) mice showed no significant increase of alveolar TGF-β activity Slpi (−/−) mice had impaired collagen gene expression but animals demonstrated minimal reduction in lung fibrosis	[91]
Human, Mice	Nasal epithelial cells (NECs) and nasal lavage fluid (NLF) from non-smokers and smokers WT and stat1 (−/−) mice.	Transcriptional regulation of SLPI expression by SLPI promoter reporter assays followed by chromatin immunoprecipitated ion.	STAT1 regulates SLPI transcription in epithelial cells and slpi protein in the lungs of mice. NECs-smokers increased STAT1 mRNA/protein expression. SLPI regulation and activity is altered in the nasal mucosa of smokers	[93]
Human, Mice	Bronchoalveolar lavage cells isolated from mild-moderate asthma (MMA) and Severe asthma (SA) patients Asthma model BALBc/ByJ, C57BL/6 J, Ifng−/− mice	IFN-γ (Th1) immune responses are exacerbated in the airways of individuals with SA, with reduced Th2 and IL-17 responses. hSLPI protein level by ELISA Gene expression by real-time PCR	Distinct immune response in SA characterized by a dysregulated IFN-γ/SLPI axis that affects lung function.	[95]
Human	Patients with severe asthma scheduled to undergo BT and bronchus biopsies	Quality of Life Questionnaire score Gene expression by real-time PCR	Subjects with Asthma Quality of Life Questionnaire score changes ≥0.5 for a period of 12 months were considered BT responders. Non-responders had score changes <0.5 for 12 months. SLPI, MMP3, and MUC19, were upregulated in responders	[98]
Human	Nasal lavage (NL) and sputum of Cystic Fibrosis (CF) patients	Microbiological analysis, cytological analysis, ELISA, cytometric bead array and FACS analysis	Concentrations of all proteases and anti-proteases were markedly higher in sputum than in NL (NE: 10-fold, SLPI: 5000-fold). NE/SLPI ratio was 726-fold higher in NL	[89]
Human	Human primary bronchial epithelial cells (PBEC) from 3 different donor culture		Both SLPI and amphiregulin secretion increased following exposure to 10 ppm diacetyl.	[99]
Human	Retrospective cohort study of patient with severe asthma	Bronchial biopsies and Gene expression by PCR	Higher levels of SLPI and lower changes in CD68 and CTGF mRNAs were observed in patients who had less than 2 exacerbations post-BT.	[97]
Human	Cystic fibrosis (CF) the upper (UAW) and lower airways (LAW) before and after intravenous- (IV-) antibiotic therapy (19 IV-antibiotic courses of 17 C F patients NL, 10 ml/nostril)	ELISA, multiplex bead array	Ratios of MMP-9/TIMP-1 were higher in sputum, and ratios of NE/SLPI were higher in NL. NE/SLPI ratio was 10-fold higher in NL compared to healthy controls.	[90]
Human	Hypoxia condition in primary human bronchial epithelial cells (1 % O_2, hypoxia)	Release of SLPI was analysed with ELISA RT-PCR	Hypoxia decreased the constitutive production of SLPI by bronchial epithelial cells. bronchial epithelial cells were exposed to exogenous TGF-β1 during normoxia, the SLPI production was down-regulated. Addition of TGF-β1-neutralizing antibodies partially restored SLPI production during hypoxia, showing that TGF-β1 is an important regulator of SLPI during hypoxic conditions.	[94]
Human	The SLPI levels in sputum from *Pseudomonas aeruginosa* infected and non-infected cystic fibrosis patients during different phases of clinical disease.	SLPI in sputum supernatants was measured by ELISA	In comparison with healthy subjects, the SLPI level in sputum was significantly reduced in all CF subjects. *P. aeruginosa* infection showed lower SLPI level than non-infected cases. Females with chronic *P. aeruginosa* infection had significantly lower sputum SLPI levels than males. Higher sputum SLPI levels were positively correlated with improved lung function.	[100]

remodelling processes were regulated by inflammation and anti-inflammatory balance [101]. Besides, common reproductive disorders were also included pyometra, which poses a risk to both future fertility and life [102–104]. Then, the biomarker that could represent evidence of this disorder is required.

In the second trimester of pregnancy, a short cervical length (CL) was a strong predictor of spontaneous preterm delivery [105]. The association between short cervical length (CL) and the level of neutrophil elastase (NE), SLPI, and IL-8 has been reported in cervical fluid. Although only cervical fluid NE level, but not SLPI, shows correlation to CL [106], but SLPI and progranulin (PGRN) concentration are positively correlated with inflammatory cytokines in cervical mucus samples from 23 to 26 weeks of gestation reflecting the risk of preterm delivery (PD). The finding from the same study in an animal model also showed a similar finding about an increase in SLPI mRNA expression in pregnant mice treated with progesterone supplement. The overexpression of SLPI exhibits anti-inflammation and results in attenuation of cervical remodelling [107]. PD is mostly found as a complication in pregnancies after *in vitro* fertilization (IVF). Serum SLPI levels can potentially be the best predictive markers for PD, similar to Human epididymis protein 4 (HE4) and IL-13 [108]. SLPI was also measured in menstrual fluids and found as one marker among five factors that moderate intraparticipant agreement, but limited variation exists in the selected proteins in menstrual fluid within and between cohorts of women [109]. Furthermore, the SLPI level in cervical mucus seems to be higher in patients with unexplained infertility when compared to the control group [110]. SLPI is also upregulated in endometrial biopsies from persistent mating-induced endometritis (PMIE) and could potentially be a diagnostic marker with 100% sensitivity and 78% specificity [111].

SLPI is crucial for embryonic development and implantation. The correlation between *slpi* mRNA expression and embryonic development progression was evaluated after the 8-cell stage. The expression of slpi mRNA was lower in *in vitro* than *in vivo* embryos. Correspondingly, *slpi* knockdown by antisense oligonucleotides diminished embryos development speed and implantation rate compared with *slpi* sense-transfected embryos and *in vitro* controls [112]. In the porcine model, a higher SLPI level was found in mid to late pregnancy than during the estrous cycle and early pregnancy [113]. Moreover, serum levels of SLPI were the second most relevant marker with 95.2% sensitivity, and 84.6% specificity at cutoff concentration of 1.3 ng/ml in canine pyometra [103,104]. Lastly, mesenchymal stem cells (MSCs) that isolated from canine umbilical cord tissue. These showed the antimicrobial peptides expression that including SLPI and active defense system (AMPs) to prevent invasion from microorganisms [114] (Table 3).

In conclusion, SLPI level was correlated with cervical length, which was a strong factor in spontaneous preterm delivery. It was also involved in embryonic development and implantation through mRNA expression levels. Remarkably, SLPI was the second-relevant marker of canine pyometra. Lastly, SLPI showed an antimicrobial effect against microorganism invasion.

4.5. SLPI in liver diseases

Acute liver failure (ALF) is not often considered nowadays, but it is reported that it is associated with high mortality without liver transplantation [115,116]. The incidence of ALF was 1.13/100,000 person-years, which was 52% women and 48% men. The point that should be considered is that the overall mortality rate within 3 months was 47% [117]. ALF can be caused by toxic, viral, and autoimmune causes [116]. Therefore, it is important to identify ALF early to refer the patient to liver transplantation.

ALF is caused by excessive hepatocyte death and innate immune response activation. Acetaminophen-induced ALF (AALF) is mostly found in ALF patient, leading to immunoparesis and innate immune response impairment [118]. SLPI in hepatic and circulatory concentrations were increased in AALF. SLPI was also expressed in biliary epithelial cells and macrophages in the necrosis area. SLPI mediated the inflammatory response in AALF by modulating monocyte and macrophage function by reducing NF-κB p65, TNF-α, and IL-6 and preserving IL-10 secretion following LPS challenge [119]. Besides, SLPI and IL-6, in plasma of the donor, were two candidates as risk-prediction biomarkers for organ donors and recipients. It has been reported that SLPI can be used as a predictive marker for liver transplantation [120] **(Table 4).**

Although studies of SLPI in the liver were not prevalent, a few studies showed SLPI was involved in inflammatory response mediation in AALF and became one of two candidate biomarkers for organ donors and recipients of liver diseases.

4.6. SLPI in kidney diseases

Acute kidney injury (AKI) is a common and increasingly complication in patients hospitalized for illness [121]. AKI occurred in one in five adults and one in three children hospitalized with acute illness, which indicated the incidence of AKI is increasing [122]. The decline in renal function that due to structural damage and impairment, leading the patient to depend on renal replacement therapy (RRT) [123]. In addition, the impact of AKI increased the risk of progression to chronic kidney disease (CKD) [124]. Therefore, markers that represent the stage of kidney injury are important.

AKI was a common complication after cardiac surgery. Biomarkers play an important role in the early diagnosis of AKI patients. It has been found that serum and urinary SLPI mRNA and protein levels significantly increase in AKI patients [125]. Urinary SLPI levels are strongly associated with SLPI mRNA levels isolated from the kidneys, reflecting organ damage associated with SLPI levels [126]. Moreover, treatment with 250 μg/kg *i. p.* SLPI could reduce elevated plasma creatinine and blood urea nitrogen (BUN) levels and tissue tubular necrosis caused by tissue damage from ischemia/reperfusion injury [127]. In kidney transplantation, SLPI concentrations in discarded cold-preservative solutions can be used as biomarkers for evaluation of the graft quality in the kidney transplant. The level of SLPI is high in delayed graft function or rejected graft post-transplant patients. In addition, SLPI could discriminate estimated glomerular filtration rate (eGFR) in low-risk patients [128]. Patients who developed AKI after thoracoabdominal aortic aneurysm repair (TAAA) showed significantly increase in serum SLPI level. Multivariable logistic regression also showed a significantly relationship between SLPI levels at 12 hours after ICU admission and AKI. The sensitivity and specificity of SLPI detection for AKI

prediction were 76.47 % and 87.5 %, respectively, with the optimal cut-off at 70.03 ng/ml at 12 hours after surgery [129]. The survival rate of kidney transplantation of decreased donors (DD) was lower than that of living donors (LD) [130]. Transcriptome analysis from kidney biopsies showed SLPI was 203 fold upregulated in DD when compared to LD, which reflected early donor injury, an acute and adaptive immune response that related to inflammation, cell death, remodelling and fibrosis [131]. In ischemia/reperfusion (I/R)-induced AKI mice suggest the potential of renoprotection underlying SLPI and SERPINA3M upregulation which is related to apoptosis and inflammation [132] (Table 5).

In brief, SLPI was highlighted in kidney diseases, especially acute kidney injury (AKI), and it was reported that SLPI was associated with early diagnosis of AKI from serum and urine by SLPI mRNA and protein expression. Moreover, urinary SLPI was also reflected in organ damage. SLPI in the preservative solution for transplantation indicated graft quality. In terms of therapeutic effect, SLPI showed attenuated creatinine, BUN level, inflammation, and apoptosis in ischemia/reperfusion injury.

4.7. SLPI and ocular diseases

The infectious endophthalmitis leads to loss of vision and eye tissue damage, which result from the inflammatory response. The most common inflammatory response was due to *Staphylococcus epidermidis* and *Staphylococcus aureus*, which are the most prevalent infectious agents [134]. Early diagnosis and treatment are essential to reducing the host inflammatory response to infection [135].

Cellular and tissue homeostasis were maintained by the balance between protease and anti-protease. The protease and antiprotease

Table 3
SLPI in urology, obstetrics and gynaecology.

Species	Study models	Readout	Outcomes	References
Human	short cervical length (CL) in the second trimester of pregnancy of women who underwent ultrasound-indicated cervical cerclage.	Levels of NE, SLPI, and IL-8 were measured by ELISA	Increased cervical fluid NE associated with cervical shortening in second trimester of pregnancy, whereas cervical fluid SLPI had constant levels.	[106]
Human, Mice	Cervical mucus samples were collected from 166 asymptomatic pregnant women at 24–26 weeks of gestation. Pregnant C57BL6 mice	Measurement of cervical length (CL) and cervical mucus sampling Measurement of PGRN, SLPI, interleukin (IL)-6, and IL-8 concentration in cervical mucus samples Association of CL with cervical mucus concentration of SLPI and PGRN proteins Masson-trichrome staining and Immunohistochemistry.	Cervical mRNA expressions of PGRN and SLPI were increased in response to progesterone supplementation and were suppressed by a progesterone antagonist, mifepristone Cervical SLPI concentrations were positively correlated with inflammatory cytokines, interleukin-6 and interleukin-8.	[107]
Human	Menstrual fluid was collected from 11 non-pregnant females with regular menstrual cycles.		Endometrial inflammatory and repair proteins were detectable in menstrual fluid supernatant, with five of eight (63%) factors demonstrating moderate intraparticipant agreement SLPI	[109]
Human	Peripheral blood was collected at day 28 of the IVF cycle	Serum assays determined by ELISA	SLPI were increased, in women who subsequently delivered preterm.	[108]
Canine	Mesenchymal stem cell (MSCs) was isolated from canine umbilical tissue	Antimicrobial peptides (AMPs) expression by reverse transcriptase PCR	MSCs from umbilical tissue showed mRNA expression of AMPs including *C*-X-C motif chemokine ligand 8 (CXCL8), Elafin (PI3), Hepcidin (HAMP), Lipocalin (LCN2) and SLPI	[114]
Canine	Clinical diagnosed of pyometra in 41 bitches	Serum level of SLPI determined by ELISA Gene expression of SLPI in the endometrium by real-time qPCR	SLPI concentration was significantly greater in the bitches those died compared to those survived. Endometrial expression of SLPI was also significantly higher in the dead group (237.61-fold) compared to the survivor group.	[103]
Canine	Cystic endometrial hyperplasia (CEH)-pyometra (CEH-P) in 25 bitches	Gene expression of SLPI in the endometrium by real-time qPCR	Endometrial transcripts of SLPI were expressed differentially in the CEH and CEH-P bitch. Serum level of SLPI was the second most relevant marker with 95.2% sensitivity, and 84.6% specificity at cut off concentration of 1.3 ng/ml, suggesting monitoring markers for management of pyometra in the bitch with critical illness.	[104]
Porcine	Crossbred gilts with randomly assigned to either cyclic or pregnant status.	SLPI mRNA expression in the endometrium by real-time qPCR Nonradioactive in situ hybridization was performed to determine the localization of SLPI mRNA expression in the endometrium	SLPI were expressed in the endometrium during the estrous cycle and pregnancy. High SLPI level found in mid to late pregnancy than during the estrous cycle and early pregnancy. SLPI mRNA primarily localized to endometrial epithelia.	[113]

balance alteration was also involved in ocular diseases, especially keratitis, corneal ulceration, and endophthalmitis [136]. In *Staphylococcus aureus* keratitis and epithelial defects of murine model showed a high level of MMP-8, IL-1, IL-6, TNF-α, and SLPI while undetectable SLPI expression occurs in the normal control corneal [137]. Similarly, Reviglio et al. reported that there is no SLPI expression in normal ocular tissues, but it can be induced by micro-organism invasion. This study showed that, SLPI expression protects rat corneal, vitreous, and retina tissue from inflammatory cells that can release proteolytic enzymes after invasion by *Staphylococcus Aureus* endophthalmitis [136,137] **(Table 6).**

Lastly, a few studies of SLPI in ocular disease reported that SLPI had a protective effect on rat cornea, vitreous, and retinal tissue from the inflammatory response that occurred due to infection. Moreover, SLPI was detected in keratitis and epithelial defects while undetectable in normal cornea.

4.8. SLPI in bone, cartilage, and dental disorders

The clinical manifestations include pain, stiffness, swelling, and limitation of joints, which are the most common chronic health outcomes of bone, cartilage, and dental disorders. These outcomes also impact mental health, sleep, work participation, and mortality [138]. The most prevalent disease due to damage of the joint tissue was osteoarthritis (OA) [139]. According to a report by GBD, 528 million people worldwide were living with OA in 2019, an increase of 113% since 1990, including 73% of OA patients older than 55 years and 60% being female [140,141]. The growing risk of OA warrants attention to timely preventive and therapeutic interventions.

Inflammation and metabolic stress can also result in bone and cartilage diseases, especially OA by upregulating the cartilage destruction [142]. Cartilage destruction was caused by the upregulating extracellular matrix degradation enzyme and/or down-regulating cartilage extracellular matrix molecules from the inflammation [143,144]. Moreover, OA-associate protease not only alters the protease enzyme activity but is also regulated by cellular inhibitory molecules, which are tissue inhibitors of matrix metalloproteinase (TIMPs) [144]. Interestingly, treatment with product of inflammation or metabolic stress in chondrocytes, including IL-1β, HIF-2α, or ZIP8, showed the upregulation of SLPI in these cells [5,145]. In addition, SLPI is specifically upregulated in OA cartilage and blood serum in both OA patients and OA mice. These findings could highlight the application of SLPI as a potential biomarker of OA [145]. Similar findings also suggest that SLPI is involved in tissue dependent release from the intra-articular human OA knee [146].

The balance between osteoclasts and osteoblasts plays an important role in the regulation of osteoporosis. Several factors have been known to be involved in bone differentiation and mineralization, including collagen I (Col I), osteocalcin (OCN), alkaline phosphatase (ALP), dentin saloprotein (DSP), dentin phosphoprotein (DPP), dentin sialophosphoprotein (DSPP), dentin matrix protein- 1 (DMP-1X), and bone sialoprotein (BSP) [147].

Furthermore, pre-treatment with recombinant SLPI on mouse osteoblast cells (MC3T3-E1 cells)accelerates adhesion and migration on Ti surfaces [148], and increases cell viability, mineralization, and pre-osteoblast differentiation. This could be due to SLPI activating upregulation of ALP, DSPP, DMP-1, BSP and Col I [149]. Similar findings have been reported in odontoblast-like MDPC-23 cells, where pre-treatment with SLPI upregulated the gene expression of BSP, OCN, Col I, osteonectin (ON), MMP-2, and MMP-9 but downregulated DSPP [150].

SLPI plays a crucial role in odontoblasts and predentin for post-natal (PN) development in mice. SLPI was expressed in odontoblasts and predentin on PN4, under dentin and the apical region on PNA10 to PN15 and under the layer of odontoblasts and in odontoblasts on PN20. This study hypothesize that SLPI may regulate MMP-2 and -9 in odontoblasts during dentin matrix formation related to differentiation and mineralization [150]. Moreover, SLPI promotes PTH-induced bone anabolism enhancing osteoblasts differentiation and increasing osteoblast-osteoclast contact [151]. In junctional epithelium (JE), odontogenic ameloblasts-associated protein (ODAM) promotes JE-related gene expression, as well as regulating the expression of SLPI [152]. SLPI is a key molecule that involved in

Table 4
SLPI in liver diseases.

Species	Study models	Readout	Outcomes	References
Human	Acetaminophen-induced acute liver failure (AALF) patients (100 ng/ml LPS from *Escherichia coli* (serotype0111: B))	White cell count (monocyte, neutrophil, lymphocyte [count3x10^9/L]) was determined by using a haematological analyser Phenotyping of Ex Vivo Fresh Blood Monocyte and Measurement of Cytokine Responses to Lipo-polysaccharide (LPS) by flow cytometer Circulating SLPI levels were assessed in sera samples by ELISA immunohistochemistry.	Hepatic and circulatory concentrations of SLPI were elevated in AALF and immunohistochemistry revealed SLPI expression in biliary epithelial cells and within hepatic macrophages (h-mψ) in areas of necrosis. H-mψ and circulating monocytes in AALF exhibited an anti-inflammatory phenotype and functional characteristics; typified by reductions in NF-κB, p65, TNF-α, and IL-6 and preserved IL-10 secretion following LPS challenge. Culture of healthy monocytes with AALF liver homogenates, plasma, or rhSLPI induced monocytes with strikingly similar anti-inflammatory characteristics which were reversed by inhibiting the activity of SLPI.	[119]
Human	Plasma of organs transplant donor	Biomarker Assays	Secretory leukocyte protease inhibitor (SLPI) was significant for predicting liver transplantation SLPI also significantly improved the predictive performance of a clinical model for liver transplantation	[120]

Table 5
SLPI in kidney diseases.

Species	Study models	Readout	Outcomes	References
Human	Acute Kidney Injury after Open and Endovascular Thoracoabdominal Aortic Aneurysm (TAAA) Repair patients	SLPI expression by ELISA	SLPI serum levels were significantly increased in patients who developed AKI.	[129]
Human	Kidney transplantation	Measure SLPI level in perfusion solution by ELISA	SLPI concentration in perfusion solution could predicts short-term organ function and complement to kidney donor, high SLPI associated with delayed graft function and rejection in first 6 months	[128]
Human	Acute kidney injury (AKI) patients and non-AKI patients	Serum and urinary levels of SLPI from acute kidney injury (AKI) after cardiac surgery by ELISA	SLPI was significantly elevated in AKI patients compared with non-AKI patients at 6 hours after surgery. SLPI was identified as a novel candidate biomarker for the early diagnosis of AKI after cardiac surgery.	[125]
Human	Renal allograft transplant (deceased donors (DD) and living donors (LD).	Transcriptome profile	This analysis revealed that SERPINA3, SLPI and CBF were up-regulated at 30 min in deceased donors (DD) compared to Living donor (LD).	[131]
Human	kidney biopsies of acute kidney injury (AKI)		Elevated transcript expression level of the SLPI in AKI allografts was confirmed in plasma and urine on the protein level	[126]
Mice and Human cell line	ischemia-reperfusion injury model) or daily administration of 60 mg/kg/day of gentamicine for 5 day (gentamicin-associated AKI model). human renal epithelium HK-2 cells (Treated with 250 μg/kg, i.p. SLPI)		SLPI reduced elevated plasma creatinine and blood urea nitrogen levels, tissue myeloperoxidase content, and acute tubular necrosis induced by kidney damage. SLPI treatment reduced CD86, CD68, CD14, CCL2, TNF-α, and IL-10 transcripts in kidney biopsies. SLPI favoured the proliferation and migration of HK-2 cells. SLPI down modulated the expression of CCL2, SLC5A3, and BECN1 but upregulated the expression of TLR4, ATF4, ATF6, HSP90B, BBC3 SLC2A1, and TNFRSF10B.	[127]
Mice	Adult congenic Mif−/−, Mif-2−/−, Cd74−/− and wild type (WT) mice on a C57BL/6 Renal ischemia reperfusion injury (IRI) in mice Mouse proximal tubular (MPT) cell lines	Evaluate of kidney damage by immunohistochemistry Serum BUN and Creatine level, RNA Seq Cell proliferation of MPT cells was assessed by 5-Bromo-2′-deoxyuridine (BrdU) and Ki67 staining assays.	MIF-2/D-DT enhances proximal tubular cell regeneration through SLPI- and ATF4-dependent mechanisms	[133]
Mice	C57BJ/6 mice Renal IR Surgery	Histologic Assessment. Haematoxylin & eosin (H&E) staining of kidney tissues, In Situ End-Labeling of Apoptotic Cells, Immunostaining of Active Caspase-3 in Kidneys, WB, PCR, Microarray	These DEGs were associated with modulated apoptosis and inflammation (upregulated BCL6, SLPI, and SERPINA3M) as well as immunity, injury, and microvascular homeostasis (upregulated complement factor H and GREM1 and downregulated ANGPTL2). This proof-of-effect study indicated the potent renoprotection of CASP3siRNA upon CHBP at the early stage of IR-induced AKI. Underlying genes, BCL6, SLPI, SERPINA3M, GREM1, and ANGPTL2, might be potential new biomarkers for clinical applications.	[132]

periodontal tissue homeostasis during biophysical force (BF)-induced tooth movement (BTM) by alveolar bone AB remodelling, by inducing osteoblastogenic genes including runt-related transcription factor 2 (Runx2), RANKL and MCSF expression, in combination with compression or tension [153]. Therefore, SLPI could be a target molecule for BTM intervention. Furthermore, PDL from healthy patients showed cytoplasmic SLPI expression that was negatively correlated to the LPS-induced stimulation of IL-6 and MCP-1 [39].

Severe congenital neutropenia (SCN) was haematological disorder that impaired promyelocutic proliferation and maturation with neutrophil count <500 cells/μL [154]. In dental pulp cells with SCN, the downregulation of ELANE and SLPI expression was evident, which consequently caused the attenuation of cell proliferation, attachment, spreading, colony formation, and wound healing with elevated reactive oxygen species (ROS), apoptosis, and inflammation [155] (Table 7).

Noticeably, SLPI was a potential biomarker of osteoarthritis that related to inflammatory response and protease enzyme activity in patient and mouse models. SLPI was involved in cell migration, adhesion, viability, bone differentiation, and mineralization. In addition, SLPI promoted osteoblast and osteoclast contact in bone anabolism. The effect of SLPI downregulation on dental cells was reported to attenuate cell proliferation and enhance ROS, apoptosis, and inflammation.

4.9. SLPI in cancer

Cancer is the second leading cause of death in the United States and has become a major public health problem worldwide. In 2022, the estimated number of new cancer cases in the United States is approximately 1,918,030 cancer cases diagnosed, which accounts for 5250 new cases each day [157,158]. In addition, 609,360 cancer deaths were occurred in the United States, that about 350 deaths per day from the lung cancer. However, the mortality patterns reflect incident trends, with declines accelerating for lung cancer, slowing for breast cancer, and stabilizing for prostate cancer [157]. The cancer mortality rate would decrease as a result of improved early detection and treatment methods and more focused cancer control activities.

Upregulation of SLPI expression has been reported in several types of cancers and its physiological roles were recently published [159]. Therefore, SLPI could potentially be an ideal biomarker for the diagnosis of cancer. Moreover, elevated levels of SLPI were also found to be involved in the metastasis ability of some cancer cells. In this part, the role of SLPI in different types of cancer will be discussed.

There are reports of high SLPI expression in colorectal cancer tissue. Knockdown of SLPI by siRNA could attenuate cancer cell proliferation, migration, and invasion that are related to the downregulation of AKT signalling [6]. An immunohistochemistry study showed that upregulation of SLPI is associated with the pathologic characteristic of colorectal cancer. This suggests that SLPI could be used an indicator of progression and metastasis in colorectal cancer patients [160].

Pancreatic ductal adenocarcinoma (PDAC) also expresses a high level of SLPI, while SLPI gene silencing showed a significant reduction in cancer cell proliferation, increased the apoptosis, and attenuated cell migration and invasion [161]. Pancreatic cancer tissue or cell lines (Bxpc-3 and Panc-1 cells) showed a high SLPI expression level. Similar to other studies, SLPI gene silencing, by shRNA-SLPI, significantly reduced cell viability, suppressed cell proliferation and induced cell apoptosis [162].

In gastric cancer, the evaluation of 68 cases of gastric cancer tissue showed high expression of SLPI, which is associated with survival time, clinical classification, and tumour size. An *in vitro* experiment confirmed that upregulation of SLPI enhances cancer cell proliferation and metastasis through regulating p53, Bcl-2, and caspase-8 expression [163].

Bioinformatics analysis and confirmation of gene and protein expression showed the downregulation of SLPI in breast cancer (BC) tissues. Moreover, SLPI levels were also negatively correlated with oestrogen receptors (ER) and progesterone receptors (PR) but positively correlated with IL-17 receptor B (IL17B) expression [164]. High SLPI secretion is also correlated with the aggressiveness of triple-negative breast cancer (TNBC) 4T1 cell. SLPI secretion was associated with spontaneous lung metastasis from 4T1 tumours orthotopically implanted in mice and worse outcome patients. Interestingly, SLPI was found to physically interact with the retinoblastoma tumour suppressor protein (Rb) and FoxM1 forms to be the Rb-FoxM1 complex. This complex released FoxM1, which might serve to activate the breast cancer metastasis targeting gene, FoxM1 [165]. A comparison of the mouse breast cancer cell line 4T1 and its highly metastatic 4T1.2 clone showed that SLPI was a dominant secreted protein highly expressed in both the medium and cell lysates of 4T1.2 cells [166]. Pre-treatment of SLPI in murine (F3II) and human (MCF-7) breast tumour cells decreased *E*-cadherin expression and re-localized to the cytoplasm, while β-catenin re-localized to the nucleus. Similarly, stable F3II overexpressing SLPI showed disrupted *E*-cadherin and β-catenin complexes that were related to the increase in Bax/Bcl-2 ratio and p21 protein level, and the decrease in *c*-Myc protein and Cyclin D1 and Claudin-1 levels [167]. This suggests the negative effect of SLPI in breast cancer.

Cancer metastasis required intravasate into the lymphatic system or vasculature and extravasate [168]. SERPINE2 and SLPI was shown to be secrete from the polyclonal mouse model, which was necessary and sufficient for vascular mimicry and ensured their

Table 6
SLPI and ocular diseases.

Species	Study models	Readout	Outcomes	References
Rat	Endophthalmitis female Lewis rats	Western blots, immunohistochemical assays, traditional culture methods.	The presence of SLPI in the inflamed cornea, vitreous, and retina tissues of rat eyes with *S. aureus* endophthalmitis	[136]
Rat	Female Lewis rats were divided into 2 groups: the infectious keratitis and the epithelial defect groups	Immunohistochemical studies	High levels of SLPI, IL-1, IL-6, TNF-alpha, and MMP-8 expression in eyes with *S. aureus* keratitis and with epithelial defects, in contrast to undetectable SLPI expression in the normal control corneas.	[137]

Table 7
SLPI in bone, cartilage, and dental disorders.

Species	Study models	Readout	Outcomes	References
Human	Protein secretomes of cartilage, synovium, Hoffa's fat pad and meniscus from knee osteoarthritis patients	Liquid chromatography tandem mass spectrometry, followed by label-free quantification. Validation of tissue-dependent protein species was conducted by ELISA on independent samples. Differential proteomes of osteoarthritic and non-osteoarthritic knee synovial fluids were obtained via similar proteomics approach, followed by ELISA validation.	70 higher abundance proteins, 23 were amongst the most highly expressed in the secretomes of a specific intra-articular tissue measured. Tissue-dependent release was validated for SLPI, C8, CLU, FN1, RARRES2, MATN3, MMP3 and TNC.	[146]
Mouse and Human	Primary-culture mouse articular chondrocytes and mouse models of osteoarthritic cartilage (OA) stimulated by destabilization of the medial meniscus (DMM) or intra-articular (IA) injection of adenovirus expressing the candidate gene	Circulating levels in human and mouse blood	SLPI was highly upregulated cellular protease inhibitor in chondrocytes treated with pathogenic catabolic factors, including interleukin (IL)-1β, hypoxia-inducible factor (HIF)-2α , and zinc importer ZIP8. Serum SLPI levels were significantly elevated in human OA patients and experimental OA mice, suggesting that SLPI may be a biomarker of OA.	[145]
Human	Human osteoblast cell line (h.FOB 1.19 cell line) treated with liposome encapsulating rhSLPI	Osteoblast adhesion, cytotoxicity, and cell proliferation by MTT assay. Osteoblast differentiation by real time qPCR.	liposome nanoparticles could encapsulate rhSLPI. For cytotoxicity, rhSLPI-LNPs treatment did not cause any toxicity to the human osteoblast cell line (hFOB 1.19). rhSLPI-LNPs could significantly enhance osteoblast adhesion, proliferation, and differentiation.	[156]
Mouse	MC3T3-E1 cells were transferred to a Ti surface with or without 1 μg/ml rhSLPI	MTT assay, PCR, Western blotting and Alizarin Red S staining	SLPI increases the viability and promotes the differentiation and mineralization of osteoblasts on Ti surfaces	[149]
Mouse	Slpi-knockout (KO) mice (C57BL/6) treated with anabolic parathyroid hormone (PTH)	Bone formation, differentiation, osteoblast-osteoclast contact	SLPI promote PTH-induced bone anabolism enhance osteoblasts differentiation, increase osteoblast-osteoclast contact	[151]

Table 8
SLPI in cancer.

Species	Study models	Readout	Outcomes	References
Human	Oropharyngeal cancer (OPC) associated with human papillomavirus (HPV)	Salivary SLPI levels in OPC cases, age, tobacco smoking and healthy from oral gargle specimens	Salivary SLPI was not associated with OPC risk but was associated with higher odds of an incomplete treatment response	[175]
Human	SLPI-deleted human gingival carcinoma Ca9-22 cells	Cell migration by microscopic imaging methods and gene expression analysis.	SLPI facilitates cell migration by regulating lamellipodia/ruffles and desmosomes, in which Galectin4 plays an important role.	[177]
Human	Human CRC cell lines (HT29 and HT116). CRC cancer tissues and matched juxtacancerous normal colorectal tissues from patients. (SLPI siRNA-mediated gene knockdown)	Cell viability by MTT assay, Cell migration and invasion, qRT-PCR	SLPI mRNA level was upregulated in colorectal cancer tissues. Targeting SLPI by siRNA inhibited proliferation, migration and invasion of colorectal cancer cells lines HT29 and HT116 *in vitro* associated with downregulation of AKT signalling	[6]
Human	Pancreatic ductal adenocarcinoma (PDAC) tissue from patient (siRNA-targeting the human SLPI gene)	qRT-PCR and Western blot, Cell proliferation and apoptosis by MTT assay and flow cytometry (FCM). The effects of SLPI knockdown on the migration and invasion by *trans*-well assays	SLPI played an important role in PDAC progression. SLPI might be an important characteristic of malignant PDAC associated with migration and invasion *in vitro* siRNA targeting to SLPI might be a potential therapeutic strategy for the treatment of PCC.	[161]
Human,	Gastric cancer, MKN28, MKN45, and GES-1 cell lines	qRT-PCR Cell proliferation ability by Cell counting Kit-8 (CCK8)	SLPI was highly expressed in gastric cancer tissues. Expression of SLPI was in significant correlation with the survival time, clinical classification and size of the tumour. SLPI could promote the proliferation and metastasis of gastric cancer by regulating P53, Bcl-2 and Caspase-8 expression through apoptosis signalling pathway.	[163]
Human	Breast cancer (BC): human tissue	SLPI expression was analysed in Oncomine online database, which was subsequently confirmed by quantitative PCR (qPCR) and Western blotting	SLPI was downregulated in breast cancer. SLPI expression was found to be negatively correlated with estrogen receptor (ER) and progesterone receptor (PR) status. SLPI expression level was decreased in negative basal-like status patients compared with positive basal-like status. Meanwhile, triple-negative breast cancer status positive correlated with SLPI.	[164]
Human	Tumour tissue and non-neoplastic mucosa from the same patients and from non-HNSCC patients.	Gene and protein expression of SLPI and gene expression of annexin 2 (a SLPI receptor), nicotine receptor (α7AChR) and arylhydrocarbon receptor (AhR) by PCR	SLPI were correlated with the patients' HPV status. SLPI gene expression in tumour tissue was higher in smokers versus non-smokers. A nicotine dependent correlation between SLPI and annexin 2 gene expression. Patients with HPV infection showed no/low SLPI expression	[172]
Mouse Human	Breast and colorectal cancer cells, lung metastasis	Identify a panel of 350 murine and 500 human secreted proteins by antibody arrays	SLPI effect on the regulation of the FoxM1 target genes and subsequent metastasis.	[63]
Mice	Polyclonal mouse model of breast tumour heterogeneity, NOD-SCID-Il2rg−/− (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ, NSG All orthotopic injections were performed using 1×10^5 mouse mammary tumour cells re-suspended in 20 μl of a 1:1 mix of PBS and growth factor-reduced Matrigel (BD Biosciences)	qPCR	SERPINE2 and SLPI were overexpressed preferentially in human patients that had lung-metastatic relapse.	[169]
Human	Prostate cancer (PCa) and bladder cancer (BCa) metastasis: PC-3, T24, UMUC3, and 293 T cell lines	VM formation assay and quantification RNA extraction and q-RT-PCR analysis Co-immunoprecipitation	Androgen receptor (AR) could differentially alter the expression of the vasculogenic mimicry (VM) marker SLPI through miR-525–5p to regulate SLPI; newly identified AR-miR-525-5p-SLPI axis may help suppress metastasis.	[181]

(*continued on next page*)

Table 8 (*continued*)

Species	Study models	Readout	Outcomes	References
Human	Human prostate cancer cell line PC-3, LNCap	Single cell RNA sequence analysis Single sample gene set enrichment analysis by ssGEA method	SLPI, VSIG2, CENPF, SLC7A1, SMC4, and ITPR2 were finally regarded as the key genes in the prognosis of patients with prostate cancer.	[182]
Human	Gastric parietal cell line (HGT-1 cells) and gastric cell lines (N87, Fu97, AGS and MKN-45 cells)	RT-qPCR The proliferation, clone formation ability, invasion, migration, apoptosis, and cell cycle of gastric cancer cells were in turn detected by CCK-8 assay, clone formation assay, transwell assay, wound healing assay, and flow cytometry analysis. The combination between LCN2 and SLPI was determined by co-immunoprecipitation assay. Western blot analysis.	LCN2 and SPLI exhibited the highest levels in AGS cells. Down-regulation of LCN2 mediated by IL-17 suppressed the proliferation and suppressed the migration and invasion and cell cycle of gastric cancer cells by targeting SLPI.	[184]
Human, Mouse	Human triple-negative MDA-MB-231, LS174T, HEK293T and MCF-7 and MDA-MB 468 cell lines 8-week-old female BALB/C mice,	Patient survival analysis Immunohistochemistry and imaging Assessment of spontaneous lung metastases	Higher SLPI expression levels correlate with worse clinical outcome in basal/TNBC patients. SLPI physically interacts with the retinoblastoma tumour suppressor protein (Rb) and releases FoxM1 from the Rb-FoxM1 complex, which may activate FoxM1 target genes involved in breast cancer metastasis.	[165]
Human	Primary human foreskin keratinocytes (HFKs) transduction with The FLAG-tagged NFX1-123 plasmid (FN123) and LXSN control vector	Real-time PCR, immune blotting	Clinical relevance of CEBPD, NOTCH1, KRT16, and SLPI, and shows the regulatory effects of 16E6E7 and NFX1-123.	[185]
Human, Mouse	Mouse (F3II) and human (MCF-7) breast cancer cells treated with rhSLPI (0.04–4 μg/ml)	SLPI levels by ELISA Protein extraction, SDS-PAGE and Western immunoblotting protocols, Immunocytochemical analysis, TUNEL assay, RNA extraction and RT-PCR procedures	Expression of SLPI was associated to a decrease in *E*-cadherin expression and re-localization of *E*-cadherin to the cell cytoplasm and β-catenin to the cell cytoplasm and nucleus, and had pro-apoptotic and cell cycle-arrest effects.	[167]
Human	Head and neck squamous cell carcinoma (HNSCC) (oral rinse collection)	SLPI was analysed using the Human SLPI Quantikine ELISA Kit	Higher concentrations of salivary SLPI might increase the risk of HNSCC among ever smokers	[173]
Mouse	Mouse breast cancer cell line 4T1, highly metastatic 4T1.2 clone female Balb/c mice (7–12 weeks of age) (Bred at the NCI Frederick were injected with 105 4T1 or 4T1.2 cells into the mammary fat pad)	Detection of SLPI by immunohistochemistry, Gene expression was determined using an Affymetrix Mouse Exon 1.0 S T gene array, RNA from the two cell lines was determined by RT-PCR	Western blotting indicated higher levels of the protein in both conditioned media and whole cell lysates of 4T1.2 cells. Higher levels of SLPI were also observed in 4T1.2 breast tumours *in vivo* following immunohistochemical staining., not detect major differences in SLPI gene expression between the 4T1 and 4T1.2 cells indicating that SLPI secretion is regulated at the protein level. secretion of SLPI is increased in highly metastatic cell in breast cancer cell line 4T1.	[166]
Human	HT-29, Ca9-22 cells and SLPI-deleted Ca9-22 cells	*In vitro* wound healing assay Analysis of mRNA expression Gene expression profiling was performed using microarray data for HT-29, wtCa9-22, and ΔSLPI Ca9-22 cells.	HT-29 cells and SLPI-deleted Ca9-22 cells showed lower migration activity than wild-type Ca9-22 cells,	[178]
Human	Colorectal cancer patients	SLPI expression by Immunohistochemistry	SLPI was overexpressed in colorectal cancer tissue. Upregulated SLPI correlates with aggressive pathologic characteristics of colorectal cancer	[160]
Human	Oral squamous cell carcinoma (OSCC) patients	protein expression analysis by immunohistochemistry.	SLPI expression correlates with lymph node metastases in the whole cohort SLPI expression correlates with overall survival (OS) and disease-specific survival (DSS).	[174]
Human and Mice	SLPI-knockout (SLPI-KO) mice and short hairpin RNA-treated cells The human adenocarcinoma cell	SLPI enzyme-linked immunosorbent assay Immunohistochemical analysis of SLPI Cytokines measurement	lung tumorigenesis induced by urethane, a chemical lung carcinogen, was significantly suppressed in SLPI-KO mice	[186]

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Table 8 (*continued*)

Species	Study models	Readout	Outcomes	References
	lines H1299 (NCI–H1299), H1650 (NCIH1650), H1975 (NCI–H1975), H358 (NCI–H358) and PC9	Detection of differentially expressed genes by microarray analysis	in association with decreased nuclear factor-kappaB (NF-κB) activity. SLPI deficiency also resulted in decreased cell numbers and decreased production of inflammatory cytokines in bronchoalveolar lavage fluids. SLPI-KO mice was associated with lower expression of NF-κB-related survival genes and DNA repair genes.	
Human	Castration-resistant prostate cancer (CRPC) and prostate cancer (PCa)	Western blot, RT-qPCR, Cell viability, Transwell invasion, apoptosis assay, ELISA, microarray data analysis, RNA-seq	Serum SLPI levels are elevated in metastatic CRPC patients compared with hormone naive patients, SLPI expression promotes CRPC cell survival and growth after androgen withdrawal *in vivo* and *in vitro*. Oncogenic effect of SLPI may be due to protection of growth factor progranulin from enzymatic cleavage or suppression of CRPC cell apoptosis independent of anti-protease activity of SLPI	[183]
Human	Oral leukoplakia patients	Correlation between the abundance of SLPI protein and the different histological grades of OL by immunohistochemistry.Biological effects of SLPI using Cell Counting Kit (CCK)-8, Annexin V/PI apoptosis assay and Caspase-Glo® 3/7 assay.	SLPI reduced in oral squamous cell carcinoma (OSCC). SLPI was negatively correlated with the histological grades of the oral premalignant lesions. SLPI promoted apoptosis in the Leuk1 and WSU-HN4 cell lines.	[180]
Human	The human pancreatic tissue specimens and peritumoral tissues were collected from 28 patients with pancreatic cancer Human pancreatic cancer Bxpc-3 and Panc-1 cell lines. (Knockout of SLPI expression was established by recombinant viral vector expressing short hairpin RNA (shRNA) targeting SLPI)	Immunohistochemistry staining for SLPI, Western blot, PCR, Cell viability by MTT, flow cytometer assay of apoptosis, cell apoptosis staining	Higher SLPI expression was observed in pancreatic tissues SLPI expression in Bxpc-3 and Panc-1 cells was effectively silenced by shRNA Silencing of SLPI expression reduced cell viability, inhibited cell proliferation, and induced cell apoptosis	[162]
Human	Myoma model Ca9-22 Uterine leiomyoma tissue, Bone marrow (BM) samples were collected at the end of the 2-day treatment and at an annual follow-up	Histochemical analysis, Gene expression profiling, Analysis of mRNA, Cell counting assay, Analysis of DNA synthesis, *in vitro* wound healing assay, Western blot, ChIP	SLPI is important for the invasion of oral carcinoma Ca9-22 cells in conjunction with MMPs. Bioinformatics analysis identified candidates as key molecules involved in SLPI-mediated tumour invasion.	[176]
Human	Head and neck squamous cell carcinoma (HNSCC), HPV positive HNSCC tissues and HPV negative HNSCC tissues were obtained from the patients who were diagnosed Human HN4 and HN30 (Cell were treated with 40 μg/ml SLPI)	RNA extraction, qPCR, Cell cycle, apoptosis analysis, cell proliferation, wound healing assay, Transwell migration and invasion assay, immunofluorescence assay, Western blot analysis, immunohistochemical analysis, NF-KB luciferase reporter gene assay	Immunohistochemical analysis conducted on HNSCC tissues illustrated that SLPI was further downregulated in HPV positive HNSCC compared to HNSCC without HPV infection. Exogenous SLPI significantly inhibited HPV E6-mediated malignant phenotypes in HNSCC cells by inhibiting the activation of NF-κB and Akt and signalling pathways	[187]
Human	Patients with papillary thyroid cancer (PTC) and multinodular nontoxic goitre (MNG).	Serum SERPINE2 and SLPI concentrations were measured using specific ELISA methods.	Significantly higher concentrations of SERPINE2 and SLPI were found in patients with PTC as compared with MNG and controls. Positive correlation was found between SERPINE2 and SLPI concentrations in PTC patients. The levels of SERPINE2 and SLPI did not differ significantly between MNG and healthy controls.	[170]
Human	Patients diagnosed with stage II/III papillary thyroid carcinoma (PTC) during 87 thyroidectomy, Tumour/normal paired thyroid tissue samples were 97 obtained from PTC patients	Gene expression profiling by DNA microarray technology. Validation of microarray data by qRT-PCR, western blot, and enzyme linked immunosorbent assay	upregulation of extracellular activities, such as proteoglycans, ECM-receptor interaction, and cell adhesion molecules, were the most prominent feature of PTC, SLPI	[171]
Human	Saliva and brush biopsies from dysplastic oral premalignant lesion	Mass Spectrometric Analysis Protein Identification and Quantification	SLPI decrease in abundance in both OPML and OSCC lesion tissues compared to	[179]

(*continued on next page*)

Table 8 (*continued*)

Species	Study models	Readout	Outcomes	References
	tissue (OPMLs) and oral squamous cell carcinoma (OSCC) patients (treated with 20 μg/mL and 40 μg/mL SLPI)	Western blot Testing Potential Anti-inflammatory Effects of SLPI Treatment on OPMLs	healthy normal tissue. SLPI decrease was observed in-vitro comparing model OPML and OSCC cell lines. In addition, exfoliated oral cells in patients' whole saliva showed a loss of SLPI correlated with oral cancer progression. *in-vitro* experiments, SLPI decreased NF-kB activity in an OPML cell line	

perfusion by the anticoagulant effect. A lung-metastasis relapse patient showed overexpression of SERPINE2 and SLPI, suggesting that these two molecules can promote metastatic progression in human cancer [169]. In addition, previous studies showed that serum SLPI and SERPRINE2 levels were higher in Papillary thyroid cancer (PTC) patients compared to multinodular nontoxic goiter (MNG) and the control group (CG) [170]. Likewise, results from DNA microarray indicated that SLPI could be a potential biomarker for PTC [171].

There was a report that showed high SLPI expression in head and neck squamous cell carcinoma (HNSCC) without human papillomavirus (HPV) driven to a greater extent in the tumour tissue of smokers than non-smokers similar to the increasing annexin A2 gene expression level [172]. It has been reported that high SLPI expression levels were associated with a higher risk of HSCC with a smoking history [173]. Interestingly, in oral squamous cell cancer (OSCC) tissue, only SLPI expression has been found in association with lymph node metastasis, overall survival (OS) and disease-specific survival (DSS) [174]. In this report, SLPI was one of fourteen biomarker protein candidates from saliva samples of OSCC that showed higher expression. In oropharyngeal cancer (OPC), although the oral gargle SLPI levels were not significantly associated with OPC, they were associated with tonsillectomy and HPV. Besides, increasing SLPI levels were also related to increasing odds of incomplete treatment response [175]. SLPI plays a role in invasion in the human gingival carcinoma Ca9-22 cell line [176]. SLPI-deleted human gingival carcinoma Ca9-22 (ΔSLPI) cells showed small lamellipodia/dorsal ruffles. The slower movement in ΔSLPI cells is associated with well-developed intermediate filament bundles in the desmosome junction compared to wtCa9-22 cells [177], and results in lower migration [178]. These studies suggest that SLPI is involved in cancer cell migration and invasion.

Contrary to the above information, SLPI downregulation has been reported to be correlated with cancer progression. Brushed biopsy samples indicated an SLPI progressive decline trend between healthy normal tissue and oral premalignant lesion tissue (OPMLs), further decreasing in OSCC lesion tissues. This indicated that a reduction in SLPI is correlated with oral cancer progression [179]. Similarly, oral leukoplakia (OL), which is the most common among oral precancerous lesions and a potential predictive tool for the malignant transformation, immunohistochemical and histological grades that are negatively correlated with the SLPI level. An *in vitro* biological effect of SLPI in human premalignant oral leukoplakia cell lines (MSK-Leuk 1) and Wayne State University-Head and Neck 4 (WSU–HN4) cell lines showed that SLPI inhibited TNF receptor-associated factor 1 (TRAF1) regulated cell apoptosis [180].

SLPI involved in bladder cancer (BCa) and prostate cancer (PCa) metastasis was altered by androgen response elements (AREs) located at different positions in the miR525 precursor promoter. AREs induce vasculogenic mimicry (VM) formation, decreasing PCa and increasing BCa metastasis through miRNA525p that altered SLPI mRNA expression [181]. AR also promote castration-resistant prostate cancer (CRPC) survival and growth, which correlate to a higher serum level of SLPI. Moreover, SLPI was associated with cancer associated fibroblast (CAFs) in prostate cancer that promotes the tumour environment [182] Therefore, SLPI promote CRPC cell survival and growth after androgen withdrawal *in vivo* and *in vitro* [182,183].

The study in the gastric cancer (AGS) cell line showed a high level of SLPI, and lipocalin-2 (LCN2). The LCN2 binding with SLPI is mediated by IL-17. Treatment with IL-17 significantly suppresses AGS cell proliferation, clone formation, migration, invasion, cell cycle and cell apoptosis by targeting SLPI [184] (Table 8).

In summary, the association between SLPI and cancer cells was different from the other diseases because the effect of SLPI involved cell proliferation, metastasis, migration, and invasion of cancer cells, which were related to an increase in SLPI levels in some types of cancer. Besides, the SLPI deficiency model showed attenuated cancer cell proliferation and migration through the Akt protein, which ensured the effect of SLPI in cancer diseases. Then, the SLPI could be a potential therapeutic target as well as biomarker of the cancer.

4.10. SLPI in metabolic diseases

Metabolic diseases are a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes, and have become a major public health issue. Although several studies have been reviewed the pathophysiology of the diseases, the roles and effects of SLPI in metabolic diseases seem not to be well-known. Only few studies demonstrate the relationship between SLPI in metabolic disorders.

The methyl-CpG-binding protein MeCP2 has been identified as a protein that selectively binds methylated DNA [188]. Abnormalities of methyl-CpG binding protein 2 (Mecp2) can be found in metabolic disorders [189]. Obese humans and mice showed upregulation of Mecp2 in white adipose tissue (WAT) that consequently binds to the SLPI promotor and regulates SLPI expression [190]. In the pathway of fatty acid metabolism regulation and lipid accumulation, fatty acid transport protein 1 (FATP1) has been

identified to be involved in the lipid metabolic pathway [154]. Studies in the model of FATP overexpression or interference by differentially expressed genes (DEGs) showed that SLPI is a candidate gene for controlling fat deposition and fatty acid metabolism [191].

Then, the study of SLPI and metabolic disorders showed only SLPI could be a candidate gene controlling fatty acid metabolism. However, further research into the relationship between SLPI and metabolic disorders is required.

4.11. SLPI in cardiovascular diseases

Cardiovascular diseases (CVDs) are considered the major cause of global mortality and disability. The pathophysiology as well as candidate treatments have been intensively studied; however, there are a limited number of studies on the roles and effects of SLPI in

Table 9
SLPI in Cardiovascular diseases.

Species	Study models	Readout	Outcomes	References
Human	Mechanisms of (EA.hy926) EC-derived human SLPI on cardiomyocytes subjected to hypoxia/reoxygenation (H/R) injury.	The cytoprotective effect was determined by cell survival assay. Intracellular reactive oxygen species (ROS) production by DCFHDA p38 MAPK pathway by Western blot analysis	EC-derived rhSLPI was increased cell viability, reduced intracellular ROS and p38 MAPK from I/R injury and H/R injury	[55]
Human	Multi-Ethnic Study of Atherosclerosis participants from four races/ethnicities (n = 2504) with protein levels measured were followed for incident AF (n = 253).		Circulating levels of SLPI were positively associated with an increased risk of incident AF in a diverse population.	[195]
Human	Blood sample from coronary artery ectasia (CAE) patients	ELISA, Bacteria endotoxin test kit	SLPI and elafin were unchanged	[194]
Human	Human umbilical vein endothelial cells (HUVECs) subjected to simulated ischemia/reperfusion (sI/R) at onset of reperfusion. (1, 10, 100 and 1000 ng/ml)	Cell viability by MTT Cellular injury by LDH assay Intracellular ROS by DCFHDA Western blot analysis Cell morphology	rhSLPI increased cell viability rhSLPI attenuated the LDH activity, ROS production. rhSLPI promoted protein kinase B activation and reduced p38 MAPK and BAX protein expression	[201]
Human	Multi-Ethnic Study of Atherosclerosis participants	Serum SLPI expression by ELISA	Serum SLPI level was associated with incident HF with preserved ejection fraction over long-term follow-up in a multi-ethnic cohort	[196]
Human	Human vascular endothelial cells (EA.hy 926) subjected to simulated ischemia/reperfusion (sI/R) in the present and absent of human serum albumin (HSA) nanoparticles encapsulated recombinant human secretory leukocyte protease inhibitor (rhSLPI)	Cell viability by MTT Cellular injury by LDH assay	rhSLPI-encapsulating human serum albumin (HSA) nanoparticles) could significantly reduce sI/R induced vascular endothelail cell injury and death.	[204]
Rat	Myocardial Ischemia/Reperfusion Injury, LAD ligation rat model treated with SLPI at during ligation and onset at reperfusion. (Treated with 50 μg recombinant human SLPI)	Infarct size, LDH, CK-MB, Inflammatory cytokines by ELISA Protein carbonylation by DNPH assay IMA level by albumin cobalt binding assay Cardiac function by pressure catheter	Post-ischemic treatments with rhSLPI *in vivo* shows cardioprotective effects against myocardial I/R injury. rhSLPI decreased infract size, LDH and CK-MB activity. rhSLPI also decreased inflammatory cytokines, ROS production and improved cardiac function.	[200]
Rat	Myocardial Ischemia/Reperfusion Injury, LAD ligation rat model treated with wild-type SLPI or mutated-SLPI at during ligation and onset at reperfusion. Cardio myoblast cell line (H9c2) (Treated with 50 μg recombinant human SLPI)	Neutrophil elastase activity by ELISA Infarct size, LDH, CK-MB, Cardiac function by pressure catheter Cell viability by MTT assay Intracellular ROS by DCFHDA	Post-ischaemic treatment of mt-SLPI shows decreased LDH and CK-MB activity. mt-SLPI decreased infarct size and improved cardiac function mt-SLPI increased cell viability and decreased intracellular ROS in H/R condition	[57]
Rat	Cardio myoblast cell line (H9c2) subjected to simulated ischemia/reperfusion (sI/R) (Treated with 400–1000 ng/ml SLPI)	Growth curve and population doubling time, cell morphology, cell injury, cell viability, intracellular ROS, WB	Overexpression of rhSLPI cells reduced sI/R-induced cell death and injury, intracellular ROS level, and increased Akt phosphorylation, rhSLPI reduced cardiac cell death and injury, and intra-cellular ROS level. SLPI inhibited p38 MAPK phosphorylation and increase Akt phosphorylation.	[53]
Rat	Cardio myoblast cell line (H9c2) subjected to simulated ischemia/reperfusion (sI/R) in the present and absent of Gelatin-coated silicon oxide nanoparticles encapsulated recombinant human secretory leukocyte protease inhibitor (rhSLPI)	Cell viability by MTT Cellular injury by LDH assay	rhSLPI-encapsulating gelatin-covered silica nanoparticles (rhSLPI-GSNPs) could significantly reduce sI/R induced cardiac cell injury and death.	[205]

cardiovascular diseases, particularly ischemic heart disease (IHD).

Protease enzymes cause widespread destruction and have relatively long half-lives in tissue [192]. Moreover, an increase in the activity of proteolytic enzymes such as chymase, matrix metalloproteinases, calpains, cathepsins, and caspases contributes to the process of cell death, and injury [193]. Therefore, the inhibition of protease activity can be considered as a powerful strategy for the prevention of ischemia/reperfusion (I/R) induced tissue injury. The levels of serum neutrophil serine proteases (NSPs) inhibitors in coronary artery disease (CAD) and coronary artery ectasia (CAE) patients were significantly increased, particularly α1-protease inhibitor (PI) and α2-macroglobin (MG). In contrast, SLPI and elafin were not significantly increased in CAE and CAD patients due to vessels being unable to serve as the main distribution sites for SLPI and elafin [194]. In addition, atrial fibrillation (AF) incident and circulating SLPI levels are positively correlated in diverse populations that are related to the circulating levels of MMP-2, TIMP-2 and VCAM-1 [195]. Additionally, serum SLPI level was also associated with incident HF with preserved ejection fraction over long-term follow-up in multi-ethnic cohort studies [196]. Several studies using *in vitro* models of myocardial ischemia reperfusion (I/R) injury, by simulated I/R (sI/R) conditions, showed that pre-treatment with recombinant human SLPI could reduce cardiac myoblast (H9c2) cell death and attenuate activation of p38 MAPK [53]. Similarly, the overexpression of the SLPI gene could also reduce cell death and cell injury [53], as well as protect the heart from an *in vivo* I/R injury [197]. This could be repetitively shown in isolated adult rat ventricular myocytes (AVRMs) [198] and isolated adult rat cardiac fibroblasts (ARCFs) [199]. The mechanisms are believed to attenuate reactive oxygen species production and the apoptosis pathway. Similar findings on the cardioprotection effect of SLPI can also be demonstrated in an *ex vivo* [198] and *in vivo* model [200] of I/R injury. Pre-treatment of SLPI or administration during LAD ligation and onset at reperfusion also showed a cardioprotective effect against I/R injury. The reduction of infarct size, improvement of cardiac function, reduction of intracellular ROS production such as protein carbonyl (PC) and ischaemic modified albumin (IMA), inflammatory cytokines and regulatory apoptotic protein are also intensively studied [200]. Interestingly, although the beneficial effects of SLPI are believed to be due to the anti-protease activity, few studies showed that those effects of SLPI might be independent of its anti-protease activity. The study of anti-protease deficiency activity of SLPI as mutant SLPI (L72K, M73G, L74G) can also provide cardioprotection against myocardial I/R injury [57]. These data suggest that SLPI has cardioprotective effects in cardiovascular diseases and especially myocardial I/R injury. Not only for the heart, but SLPI can also provide vasculo-protection on vascular endothelial cells [201] against an *in vitro* simulated ischemia/reperfusion (sI/R) injury. The similar mechanistic findings have been reported by reducing cell death, intracellular ROS production, attenuating the apoptotic pathway, and enhancing the cell survival pathway. SLPI that is derived from vascular endothelial cells could be an angiocrine that reduces cardiac cell death [55]. Therefore, the application of SLPI as a cardio-vasculo protective agent could be possible. Previous work from Schneeberger et al., in 2008, showed that the addition of the recombinant protein of SLPI in a preservative solution could restored myocardial contraction in a transplanted heart [202]. Similarly, an isolated thoracic aorta and abdominal aorta ring preserved in a normal saline solution supplemented with recombinant protein of SLPI could reduce vessel graft inflammation and tissue degeneration [203]. These studies suggest a cardioprotective effect of SLPI and it could potentially be a candidate for new drugs (Table 9).

Remarkably, SLPI in cardiovascular diseases showed both biomarker potential in AF patients and HF-preserved EF patients and therapeutic effect against I/R and H/R injury. In detail, SLPI attenuated cell injury, cell death, reactive oxygen species, and oxidative stress production in *in vitro*, *ex vivo*, and *in vivo* models.

5. Perspective view and future application of SLPI in NCDs

Based on the present research, it is evident that the SLPI has promising attributes as a therapeutic candidate, therapeutic target, and biomarker for several non-communicable diseases (NCDs). This section presents a discussion on several perspectives concerning the use of SLPI in the field of biomedicine.

5.1. SLPI as a novel therapeutic candidate

Excessive protease activity is frequently observed in the context of inflammatory conditions affecting several organ systems, coagulopathy, cancer advancement, neurological disorders, metabolic dysregulation, and cardiovascular pathologies. The protease inhibitory activity of SLPI appears to alleviate tissue damage and inflammation through the inhibition of proteases, since the therapeutic potential of overexpressing the SLPI gene or administering exogenous recombinant SLPI protein has been identified [53,197].

While it is well acknowledged that SLPI has the ability to hinder proteases, which is thought to account for its positive impact, several studies have indicated that the anti-protease activity of SLPI may not be essential [57]. This suggests that the observed positive impact of SLPI may be attributed to the direct influence of SLPI molecules. The direct pharmacological actions of SLPI encompass several beneficial outcomes, such as anti-apoptosis, cardioprotection, and osteoblast differentiation [156,200]. The direct therapeutic effect of SLPI may be mechanistically explained by its association with other binding partner molecules, such as annexin A2 [25] or scramblase 1 and 4 [16]. The further research of identifying additional binding partner molecules and downstream signalling pathways that are specific to a particular illness remains a significant challenge. To mitigate any side effects associated with SLPI therapy, it is imperative to possess a comprehensive comprehension of the partner molecules involved and the signalling mechanisms at play.

One of the primary constraints in using SLPI as a therapeutic agent in clinical settings is the inherent instability of SLPI. Prior research has indicated that SLPI was found to exhibit a rapid elimination rate in both human plasma and urine. SLPI is typically cleared from the body by glomerular filtration, followed by reabsorption and breakdown in tubular cells. Within the time frame of 2–6 hours, the estimated half-life of SLPI in plasma is reported to be 120 min [29]. Additionally, it has been observed that enzymes present in the respiratory tract, such as cathepsin [206], are responsible for the inactivation of SLPI. Hence, the implementation of a strategic

approach aimed at enhancing the stability and prolonging the half-life of SLPI within the system might potentially provide significant therapeutic advantages. Further work is required to thoroughly examine the transport of therapeutic SLPI protein to particular target cells or tissues. The field of biomedical engineering and drug delivery has witnessed significant progress, with notable developments such as the introduction of nanoparticles as carriers for peptide medications. These nanoparticles have demonstrated several benefits, including the reduction of enzymatic digestion and aggregation of peptide pharmaceuticals, as well as an enhancement in transmembrane absorption. Further investigation is required to determine the effectiveness of nanoparticle delivery of SLPI in each illness model. Prior research has documented three distinct categories of nanoparticles that have successfully contained SLPI. In a study conducted in 2009, Gibbons A. et al. used liposome nanoparticles as a method for encapsulating SLPI, aiming to offer defence against cathepsin L digestion inside the pulmonary system [207]. Liposome nanoparticles have substantial efficacy in safeguarding against the degradation of cathepsin L, hence revealing a notable level of effectiveness of secretory leukocyte protease inhibitor (SLPI). In 2011, liposomes were utilised as a carrier for encapsulating SLPI in an experimental asthma model. Liposomes have been observed to provide a protective effect on the elimination of SLPI in the systemic circulation, hence functioning as stable and protective carriers for inhalation [208]. The use of alginate/chitosan nanoparticles for the application of SLPI in pulmonary contexts was described in a study conducted by Hill M. et al., in 2019. According to the findings of the study, it was observed that the co-administration of Tobramycin and SLPI demonstrated antibacterial characteristics and improved the efficiency of medication administration over prolonged periods [209]. The findings of Tarhini M. et al. (2020) were published in research that examined the utilisation of human serum albumin (HSA) nanoparticles as carriers for encapsulating SLPI, with the objective of creating an antibacterial agent. Prior research has demonstrated that the antimicrobial and anti-neutrophil elastase (NE) properties of secretory leukocyte protease inhibitor (SLPI) are unchanged when it is enclosed within human serum albumin (HSA) nanoparticles [210]. In a recent study conducted by Phutiyothin C. et al., it was observed that HSA (human serum albumin) has been used as a double-coated layer for the purpose of delivering rhSLPI (recombinant human secretory leukocyte protease inhibitor) in order to mitigate vascular endothelial cell damage [204]. Chouyratchakarn et al. (2022) conducted a study in which they found that liposomes loaded with recombinant human secretory leukocyte protease inhibitor (rhSLPI) had the ability to stimulate the proliferation and differentiation of human osteoblast cells (hFOB 1.19). Additionally, these liposomes were seen to enhance the adherence of osteoblasts to the substrate surface [156]. In a study conducted by Pikwong F. et al., it was stated that silica nanoparticles coated with gelatin were used for the encapsulation of SLPI in order to mitigate cardiac cell damage and mortality resulting from ischemia/reperfusion (I/R) conditions [205].

5.1.1. SLPI as a novel therapeutic target

The SLPI can be "a double-edged sword" as it possesses both positive and negative implications within the realm of illness causation. The advantageous functions of SLPI under many pathological circumstances are counterproductive in these illness models. The involvement of the SLPI's regulatory role has been associated with the development of many malignant illnesses. Recent studies have demonstrated that the increasing levels of SLPI within cancer cells may augment the metastatic capacity of tumours, hence substantiating the detrimental consequences connected with this phenomenon. Given the potential involvement of SLPI in carcinogenesis, cancer development, and metastasis enhancement, it is worth considering therapeutic strategies that target the expression and secretion of SLPI as a promising and innovative therapy method. Downregulation of SLPI, by means of gene silencing or slpi knock out transgenic animal, has been demonstrated to suppress the carcinogenesis and metastasis ability in several cancer model [6,211–213]. In addition, SLPI was identified as a novel resistance factor to Cisplatin in colorectal cancer [212]. The administration of a chemotherapeutic medication in conjunction with the suppression of secretory leukocyte protease inhibitor (SLPI) may offer potential pharmacotherapeutic advantages. Given the discussion around the beneficial outcomes of SLPI as a therapeutic agent, it becomes imperative to exercise caution when contemplating the inhibition or downregulation of SLPI for the purpose of cancer therapy. Additionally, it is imperative to emphasise the importance of caution regarding the extended utilisation of SLPI as a therapeutic medication in order to mitigate the occurrence and advancement of tumours.

5.1.2. SLPI as a novel biomarkers (diagnosis, monitoring, prognostic)

Biomarkers serve as indications of common biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions. So, biomarkers possess the potential to be employed in the identification, prediction of outcome, and therapeutic management of many medical conditions. Previous studies have shown alterations in the expression levels of the SLPI gene and protein in various tissues and bodily fluids, indicating their potential as biomarkers [159]. The involvement of SLPI in the process of carcinogenesis implies that alterations in SLPI expression levels may serve as potential biomarkers for a range of malignancies, such as breast cancer, lung cancer, ovarian cancer, and head and neck cancer [159]. In addition to the increase of SLPI expression levels in malignant tissues, alterations in SLPI levels in bodily fluids, including blood and saliva, have demonstrated potential in discerning the existence of cancer [159]. Consequently, these changes might serve as valuable indicators for early cancer diagnosis and monitoring of disease progression.

Elevated levels of secretory leukocyte protease inhibitor (SLPI) in biological tissue or fluid have been seen in non-malignant illnesses, suggesting the potential use of SLPI as a biomarker. The use of SLPI as a potential biomarker for acute kidney damage (AKI) has been investigated in the context of cardiac surgery [125] and thoracoabdominal aortic aneurysm repair (TAAA) [214]. Patients who have been diagnosed with acute kidney injury (AKI) have higher levels of serum and urine secretory leukocyte protease inhibitor (SLPI) within 24 hours after undergoing surgery. The sensitivity and specificity of SLPI for predicting AKI in patients with TAAA were found to be 76.47% and 87.5%, respectively, at the 12-hours postoperative mark. This finding suggests that SLPI has potential utility as prognostic or risk assessment indicators.

SLPI levels in sputum can be altered, and monitoring the SLPI levels may help assess disease severity and progression of cystic

fibrosis [100], Chronic obstructive pulmonary disease (COPD) and asthma [215]. A decreased level of sputum secretory leukocyte protease inhibitor (SLPI) may serve as a reliable marker for worse prognosis in respiratory conditions. The monitoring of SLPI can be conducted in conjunction with other biomarkers, such as the reduction in β-defensin-1 level and the rise in neutrophil elastase. These biomarkers may serve as indicators for identifying patients experiencing a decline in lung function in the context of cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and asthma, respectively. In allergic rhinitis (AR) and asthmatic airway disease, cleaved portion, cSLPI, is a biomarker of chymase activity in patients. As previously indicated in this review, it has been suggested that SLPI may be susceptible to cleavage by an alternative protease, such as chymase [28]. The study examined the ratios of cleaved-SLPI (cSLPI) to SLPI and the levels of chymase, as well as the ratios of cSLPI to SLPI and the level of alpha2-macroglobulin [216].

Elevated levels of salivary SLPI may also serve as an indicator of pathological conditions and the potential for developing diseases. There is a strong correlation between elevated levels of salivary secretory leukocyte protease inhibitor (SLPI) and reduced rates of HIV-1 transmission, whereas conversely, low levels of SLPI in mature breast milk are associated with insignificant rates of transmission [67, 217]. Elevated levels of SLPI may serve as a potential predictor of periodontal health. Notably, these levels are shown to be further increased in individuals with gingivitis, but thereafter drop in cases of severe periodontitis, surpassing the levels observed in both gingivitis and periodontitis [218]. Additionally, it has been suggested that elevated levels of salivary SLPI may potentially heighten the susceptibility to head and neck squamous cell carcinoma (HNSCC) in those who smoke [173].

Due to its ease of accessibility and less intricate composition compared to serum or plasma, tears have emerged as a subject of research for the discovery of biomarkers related to ocular illnesses. The SLPI protein has been recognised as a promising candidate for use as a biomarker in the diagnosis and monitoring of various eye diseases. Elevated levels of secretory leukocyte protease inhibitor (SLPI) were seen in individuals diagnosed with primary Sjogren's syndrome (SS) [219]. The use of proteomic analysis revealed an upregulation of SLPI in individuals diagnosed with dry eye, whereas a downregulation of these proteins was observed in patients with Meibomian gland dysfunction (MGD) [220] and Thyroid-associated orbitopathy (TAO), and Graves' disease with and without orbitopathy [221].

An intriguing illustration of the use of SLPI as a biomarker is shown in the elevation of SLPI levels within cervical mucus. The aforementioned biomarker has the potential to serve as a valuable predictor of the duration of spontaneous delivery in uncomplicated, nulliparous pregnancies characterized by an unfavourable cervix [222]. Moreover, it has been observed that there is a correlation between elevated levels of serum secretory leukocyte protease inhibitor (SLPI) and interleukin-6 (IL-6) in cases of uterine infection and the subsequent development of pyometra. This correlation may be utilised to predict the occurrence of sepsis in pyometra, indicating the potential of SLPI as a predictive biomarker in the field of obstetrics and gynaecology [102].

It is evident that the changes in SLPI levels seen in clinical samples are indicative of pathological disorders. The identification of SLPI has the potential to serve as an innovative biomarker for the purposes of diagnosing, monitoring, stratifying risk, and determining prognosis. The restricted tissue specificity of SLPI expression in many organs hinders its potential as a diagnostic marker, hence restricting its utility as a standalone biomarker. Therefore, the combination of SLPI detection alongside other diagnostic procedures has the potential to augment the sensitivity, specificity, and effectiveness of biomarkers. Additional rigorous clinical study, in large multicentre study, is required to assess the clinical efficacy of SLPI in various disorders.

6. Conclusion

This review article presents empirical information about the pathophysiological functions of SLPI in non-communicable diseases (NCDs) across many experimental models. Furthermore, this article also proposes the advantageous impacts of SLPI as a therapeutic agent, therapeutic target, and new biomarker for NCDs. The implications derived from this analysis will contribute to the identification of a novel therapeutic target and diagnostic marker for non-communicable diseases. Further research focusing on enhancing of specific organ targeting of SLPI as a therapeutic agent, targeted inhibition of SLPI for therapy, and also the improvement of diagnosis efficacy of SLPI as biomarker for NCDs need to be intensively studied.

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Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Sarawut Kumphune reports a relationship with Chiang Mai University that includes: employment and funding grants. Podsawee Mongkolpathumrat reports a relationship with Thammasat University that includes: employment. Sasimanas Unnajak reports a relationship with Kasetsart University that includes: employment and funding grants. Nitirut Nernpermpisooth reports a relationship with Naresuan University that includes: employment and funding grants. Faprathan Pikwong, Chayanisa Phutiyothin, Onnicha Srisopar, Wannapat Chouyratchakarn reports a relationship with Chiang Mai University that includes: funding grants. If there are other authors, they 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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