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TITLE: Secretory Leukocyte Peptidase Inhibitor (SLPI) functionality in health and disease

Abstract

Secretory Leukocyte Peptidase Inhibitor (SLPI) is a serine protease inhibitor of cathepsin G, trypsin and chymotrypsin, but primarily against neutrophil elastase. Its major function is to inhibit inflammation by blocking the proteolytic activity of these proteinases released by leukocytes and also through down-modulation of several cytokines. The anti-inflammatory activity is also mediated by inhibition of the activation of the transcription nuclear factor NF-kB. Some studies localized the molecule within the cytosol and in secondary granules of neutrophils. Because of this, it is believed that neutrophil-derived SLPI may regulate the protease/antiprotease balance at sites of tissue inflammation. In relation with the adaptive immune system, it was suggested that SLPI modulates the cellular and humoral immune response, by decreasing the T cell proliferation and reducing the class switching. Also, it is known that this polycationic non-glycosylated peptide, displays anti-microbial properties against bacteria, viruses (in particular HIV) and fungus. In summary, the SLPI is a pleitropic molecule, implicated in physiological and pathological events, such as wound healing, pregnancy, chronic obstructive pulmonary disease, cancer, ischemia reperfusion injury and stroke, among others. Their detection in serum and biological fluids may be useful as a biomarker to diagnosis and prognosis for certain diseases.

Keywords: SLPI, antimicrobial activity, anti-inflammatory activity, anti-tumoral activity.

IDENTITY

Gene name: SLPI

Alias: Secretory leukocyte protease inhibitor (SLPI)
Antileukoproteinase (ALK1, ALP)
Human Seminal proteinase inhibitor (HUSI, HUSI-I)
Bronchial leukocyte proteinase inhibitor (BLPI)
Mucus proteinase inhibitor (MPI)
Whey-acidic-protein 4 (WAP4)
WAP four-disulfide core domain protein 4 (WFDC4)

Hugo name: secretory leukocyte peptidase inhibitor
Hugo symbol: SLPI
Location: 20q13.12 (Start: 45,252,239 bp from pter and End: 45,254,564 bp from pter)
Chromosome Location: chr20:43,881,055- 43,883,184 (reverse strand)
Locus Type: gene with protein product

DNA

SLPI belongs to the whey acidic protein four-disulfide core family of proteins. The human SLPI gene is localized on chromosome 20q12-13.2 (Kikuchi et al. 1998). The SLPI gene consists of four exons and three introns, it spans approximately 2.6 kb (Kikuchi et al. 1998; Stetler et al. 1986). The SLPI gene is stable and seems to be nonpolymorphic (Abe et al. 1991). Though, it has the potential to be modulated at both the transcriptional and post-transcriptional levels (Abe et al. 1991). Up to date, it has not been detected a state of SLPI deficiency. However, patients with severe congenital neutropenia (a primary immunodeficiency syndrome characterized by mutations in at least 6 different genes) were found to have strongly reduced SLPI levels, being SLPI a key factor for the neutrophil differentiation in the bone marrow (Klimenkova et al. 2014).

TRANSCRIPTION

The SLPI gene is actively transcribed in mucosal cells, being the half-life of the transcripts of approximately 12 h. Close to the exon 1, SLPI gene has four potential binding sites for transcription factor AP-1, three for AP-2 and one for C/EPB(Klimenkova et al. 2014). Also, Kikuchi *et al.,* describes that SLPI has a promoter region which has a recognition sequence for two transcription factor, one of which is highly expressed in lung cell lines, and the other in nonlung cell lines (Kikuchi et al. 1997).

PROTEIN

SLPI is an 11,7 kDa molecular weight non-glycosylated protein composed by 132 amino acids (Stolk et al. 1999). The amino acid sequence of SLPI generates a highly polycationic peptide with two highly homologous domains. These two domains (COOH and NH2 terminal domains) share around a 35% homology (Vogelmeier et al. 1996). Each domain contains eight cysteine residues that form four disulfide bonds, which helps to stabilize the structure of the molecule (Grutter et al. 1988). These cysteine rich domains are also called WAP domains (Whey Acid Protein). Domain 2 was initially described to bind and inhibit the serine proteases such as trypsin and elastase, while the domain 1 was probably not inhibitory (Eisenberg et al. 1990; Meckelein et al. 1990). It has been proposed that this last domain helps in the stabilization of the complexes “SLPI:elastase”. Also, it is believed that the domain 1 mediates binding to heparin, and thus increases its antiprotease activity, probably as a result of a conformational change of the molecule. (Faller et al. 1992).

EXPRESSION

SLPI was first isolated from bronchial secretions (Hochstrasser et al. 1972; Ohlsson et al. 1976). Then the SLPI was characterized by two groups of researchers, whom purified the molecule from the urine and (Seemuller et al. 1986) and the parotid gland secretions (Thompson et al. 1986). SLPI is located in both, the extracellular matrix and the intracellular compartments, suggesting that it could exert autocrine and paracrine effects (Taggart et al. 2005).

The expression of SLPI is constitutive as well as modulated by different factors. Constitutively SLPI can be found in serum and in extravascular mucosal fluids. Thus, it is found around of 40 (26.1–65.0) ng/ml in serum, 72 (0.4–250) ng/ml in bronchial lavage fluid (Hollander et al. 2007), in exhaled breath condensate (2.82 ± 0.58 pg/ml)(Tateosian et al. 2012) and saliva (0.3-3.2 ug/ml) (Shugars et al. 2001). However, concentrations of the molecule vary depending on age and gender of the individual tested. *In vivo*, it is produced in the lung by tracheal serous glands and by clear bronchial cells. In male (Ohlsson et al. 1995) and female (Moriyama et al. 1999) genital tracts, SLPI is located in seminal plasma and cervical mucosa, respectively. Furthermore, it is produced by the parotid glands, intestinal epithelial cells (Si-Tahar et al. 2000), renal tubule cells (Ohlsson et al. 2001), keratinocytes (Wiedow et al. 1998), β cells of the pancreas (Nystrom et al. 1999) and immune cells like neutrophils and alveolar macropaghes (Sallenave et al. 1997; Mihaila et al. 2001; Guerrieri et al. 2011).

The SLPI expression is modulated by different molecules. It has been shown that SLPI is up-regulated by LPS, IL-1β, TNF-α, neutrophil elastasa, α-defensins, surfactant protein A, corticosteroid and progesterone (Sallenave et al. 1994; Reid et al. 1999; Maruyama et al. 1994; Abbinante-Nissen et al. 1995; King et al. 2003; Velarde et al. 2005; van Wetering et al. 2000; Ramadas et al. 2009). Finally, apoptotic cells can upregulate SLPI production by macrophages (Odaka et al. 2003). In contrast, few factors can downmodulate the expression of SLPI. Among them, the most significant are IFNγ and TGF-β (Jaumann et al. 2000; Jin et al. 1997).

Although, the structure of SLPI seems to be stable, it could be cleaved and inactivated by chymase(Belkowski et al. 2008), cathepsins B, L, S (Taggart et al. 2001), lipid peroxidation products (Tomova et al. 1994) and Host dust mite 1 allergen (Brown et al. 2003), among others(Weldon et al. 2009).

FUNCTIONS

Antiprotease activity: The inhibition of protease activity was described for C-terminus domain against elastasa, cathepsin G, trypsin, chymotrypsin, tryptase and chymase (Williams et al. 2006). Thus, SLPI major function is inhibit inflammation by blocking the proteolytic activity of serine proteinases released by leukocytes and also through blocking the LPS effects, such as the upregulation of several cytokines like TNFα, MCP-1 and IL-6 (Yang et al. 2005; Jin et al. 1998; Taggart et al. 2005; Ashcroft et al. 2000). SLPI acts locally to maintain a protease/antiprotease balance thereby preventing protease mediated tissue destruction (Vogelmeier et al. 1990). In the lungs, the disturbance of this balance is responsible for various lung diseases, many of which are initiated and maintained by the recruitment and activation of neutrophils (Birrer et al. 1994; Suter 1989).

Anti-inflammatory activity: SLPI has anti-inflammatory activities not necessarily related to its ability to inhibit extracellular proteases. The anti-inflammatory activity is also mediated by inhibition of proteolytic degradation of IkB, an inhibitor of the nuclear factor NF-κB (Ashcroft et al. 2000; Samsom et al. 2007). It has been shown that over-expression of SLPI inhibits NF-κB, which is a transcription factor of several pro-inflammatory mediators in pulmonary inflammation (Henriksen et al. 2004). Currently, there are some evidence that SLPI is rapidly taken up by cells and is localized in the nucleus and cytoplasm (Taggart et al. 2002). In the cytoplasm, SLPI prevents degradation of several key proteins in the regulated activation of NF-kB, as IκBα, IκBβ and IRAK (IL-1-receptor-associated kinase) through the ubiquitin-proteasome mechanism (Greene et al. 2004; Taggart et al. 2002), that follows the activation of NF-kB by LPS or LTA (lipoteichoic acids). Also it has been proposed that SLPI acting in the nucleus can bind to NF-κB consensus region of target genes (Taggart et al. 2005). The entering into the nucleus occurs through a mechanism in which SLPI may traverse membranes, due to its cationic nature (favored by the high content of arginine and lysine) by interaction with the negatively charged membrane. Independently of the mode of action, *in vivo* experiments have demonstrated anti-inflammatory / pro-apoptotic activities in the lung, and in a variety of other organs.

Microbicidal activity:

Against Bacteria: SLPI displays anti-microbial properties *in vivo* and *in vitro* (Sallenave 2002; Gomez et al. 2009). It has been recently reported that mouse and even human SLPI shows anti-bacterial activity against mycobacteria and it constitutes a pattern recognition receptor (PRR), that not only kills the microorganism, but also facilitates their phagocytosis by murine and human macrophages (Nishimura et al. 2008; Gomez et al. 2009). Either the antimicrobial activity or PRR ability depends on the COOH terminal domain where the inhibitory activity of serine proteases resides. The WAPs domains of the molecule are involved, and this is due to cationic residues that allow the disruption of the membranes of target organisms (Verma et al. 2007; Gomez et al. 2009; Nishimura et al. 2008). The antimicrobial activity of human SLPI has been described for various bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermis* (Wiedow et al. 1998; Wingens et al. 1998), *Mycobacterium tuberculosis* (Gomez et al. 2009), and *Escherichia coli* (Williams et al. 2006). Therefore this activity is against Gram negative and Gram positive bacteria and is part of the defense system of the mucosa.

Against Viruses: SLPI has been suggested as the main soluble factor responsible for the HIV inhibitory effect of saliva. It is well-established that human saliva inhibits HIV infectivity in vitro (McNeely et al. 1995; Nagashunmugam et al. 1997; Shugars et al. 2001; Malamud et al. 1992; Fultz 1986). The infection of adherent primary monocytes with HIV-1 was significantly suppressed in the presence of human saliva [76-80]. Four in vitro studies have demonstrated that SLPI has anti-HIV-1 activity in cells that included peripheral blood mononuclear cells, purified primary T cells, and SupT1 cells, a lymphocyte-derived tumor cell line (Fultz 1986; Hocini et al. 2000; Shugars et al. 1997; Skott et al. 2002). Evidence suggests that SLPI blocks HIV-1 internalization in a dose-dependent manner (McNeely et al. 1997). McNeely *et al*. found that SLPI inhibits a step of viral infection that occurs after virus binding but before reverse transcription. In a co-precipitation experiment, it was described a 55-kDa cell surface protein from monocytes by using anti-SLPI antibodies. For some authors, the interaction between HIV and CCR5 could be the main target of SLPI (Naif et al. 1998). Other authors showed that SLPI interferes with HIV fusion with the T-cell plasma membrane through binding to scramblase 1, a membrane protein that interacts with CD4 and controls the movement of the phospholipid bilayer of the plasma membrane (Shugars et al. 1999). It was also demonstrated that in myeloid cell, SLPI blocks viral entry/fusion as a result of binding to annexin II (Ohlsson et al. 2001; Ma et al. 2004; Drannik et al. 2011). This molecule is a macrophage receptor that binds to phosphatidylserine moiety that HIV carries on its outer layer on exiting from an infected cell (Ohlsson et al. 2001; Drannik et al. 2011; Ma et al. 2004). Furthermore, the elastase inhibiting activity of SLPI was not be essential for their anti-HIV-1 activity (McNeely et al. 1997).

Against Fungi: *C. albicans* and *Aspergillus fumigatus* were sensitive to the antimicrobial activity of recombinant SLPI. This activity was localized to N-terminal domain of the molecule (Tomee et al. 1997).

Wound healing activity: The role of SLPI in tissue repair was suggested by the observation that in human, epithelial expression of SLPI is increased in damaged skin (Wingens et al. 1998). Studies in SLPI deficient mice demonstrated that SLPI has an essential role in wound healing (Ashcroft et al. 2000). In the absence of SLPI, the animals presents a delay in cutaneous wound healing, which is attributed to an increased and prolonged inflammatory response during the repair process, and a delay in the accumulation of the matrix. The altered inflammatory profile involves enhanced activation of local TGF-β (Ashcroft et al. 2000).

Immunomodulatory activity in adaptive immune response: The effect of SLPI seems not to be limited to innate immune response but also to the cellular and humoral adaptive immune response. In fact, the high SLPI expression was found in dendritic cells of mucosal lymph node and it was suggested that these dendritic cells regulate cellular activation to microbial products and maintain the tolerance threshold (Samsom et al. 2007). Also, we have observed that SLPI decreases lymphocyte proliferation, a phenomenon which depends on the presence of monocytes (Guerrieri et al. 2011). However, it is not possible to rule out a direct effect of SLPI on lymphocytes since it is able to bind the receptors phospholipid scramblases 1 and 4 on CD4 T cells (Py et al. 2009). On tonsillar cells, SLPI inhibits B cells expressing activation-induced cytidine deaminase, an enzyme involved in class switching. Thus, the overall idea is that SLPI is a tolerigenic factor, that it is able to down modulate the innate and adaptive immune response. Moreover, recently it has been shown that the hyporesponsiveness of human buccal epithelium to microbial stimulation is a phenomenon that depends on SLPI expression. (Menckeberg et al. 2015).

Recently, it has been also described that SLPI, in conjunction of neutrophil DNA or cathepsin G and human neutrophil elastase, induced a marked production of type I interferon by plasmacytoid dendritic cells (Skrzeczynska-Moncznik et al. 2012; Skrzeczynska-Moncznik et al. 2013). On the other hand, it was found that SLPI inhibits the formation of neutrophil extracellular traps; structures that are involved in the elimination of microorganisms, and also in the presentation of autoantigens (Zabieglo et al. 2015). These findings suggest a role of SLPI in autoimmune diseases.

Physiological and pathological implication

Pregnancy

SLPI among others antimicrobial peptides seems to play a role in pregnancy. SLPI is produced by amnion epithelium and deciduas (King et al. 2007). High levels of SLPI were found in the cervical mucus plug during human pregnancy. The SLPI mRNA expression was higher in the second and the third trimester when compared with the first one (Itaoka et al. 2015). Thus, in amniotic fluid, its concentration increases according to the period of pregnancy and the highest levels is reached on the onset of labor (Denison et al. 1999). As SLPI is a natural antimicrobial molecule, it may be involved in the prevention of uterine infection during pregnancy and labor, and be a modulator of inflammation in this stage.

Autoimmunity

High levels of SLPI have been observed in several autoimmune diseases. For example, it was observed in: i) inflamed joint tissues in a rat model of arthritis (Song et al. 1999); ii) patients with primary Sjögren's syndrome (Maruyama et al. 1998); iii) immune cells infiltrating the corpus in autoimmune gastritis (Hritz et al. 2006); iv) macrophages, activated microglia, neuronal cells and astrocytes during experimental autoimmune encephalomyelitis (Mueller et al. 2008).

In contrast, the administration of systemic SLPI or microencapsulated SLPI has proven to reduce the injury found in tissues of different autoimmune models (Guazzone et al. 2011; Song et al. 1999). Overall, these results highlight the in vivo immunosuppressive effect of SLPI. However, it has been also implicated in the pathogenesis of other autoimmune diseases such as psoriasis. As we mentioned above, Nestle et al. have demonstrated that the IFNα, produced by plasmacytoid dendritic cells in response to DNA structures, containing the neutrophil serine protease cathepsin G (CatG) and SLPI was important in the development of psoriatic skin lesions (Skrzeczynska-Moncznik et al. 2013). In fact, the neutralization of SLPI reduces the severity of experimental autoimmune encephalitis (Muller et al. 2012).

Tuberculosis

Exposure of murine peritoneal macrophages to Mycobacterium tuberculosis led to an increase in SLPI protein secretion (Ding et al. 2005) which seems to be a pattern recognition receptor for micobacterias and inhibits the growth of them(Nishimura et al. 2008; Gomez et al. 2009). In plasma of tuberculosis patients, the SLPI and IFN-γ levels were significantly higher compared with the levels found in healthy subjects. Moreover, a direct association between SLPI levels and the severity of tuberculosis was detected. The main protective cytokine in tuberculosis, IFN-γ, decreased the expression of SLPI in healthy subjects but not in tuberculosis patients, probably because of the low expression of IFN- γR detected in these patients (Tateosian et al. 2014).

Chronic obstructive pulmonary disease (COPD)

Emphysema may be due to an imbalance in protease-antiprotease activity. Patients with COPD show high levels of SLPI compared with healthy subjects (Hollander et al. 2007). Conversely, SLPI levels are decreased during COPD exacerbations produced by bacterial infection or rhinovirus (Mallia et al. 2012).

Cancer

The invasiveness of tumors occurs through infiltration of tumor cells into healthy tissue and by angiogenesis, which is modulated by proteases and antiproteases released from tumor cells that carry out tissue remodeling. Many studies have shown that SLPI expression is modulated in cancer. However, there has been reported an increased or decreased expression profile of the protein depending on the type of tumor. For example, SLPI expression is increased in pancreatic (Iacobuzio-Donahue et al. 2003), thyroid (Jarzab et al. 2005), cervix (Rein et al. 2004), endometrial (Zhang et al. 2002), ovarian (Israeli et al. 2005) and gastric cancer (Cheng et al. 2008). In contrast, it is weakly expressed in nasopharyngeal carcinoma (Sriuranpong et al. 2004; Huang et al.

2012), bladder tumors (Liang et al. 2002) and some breast carcinomas (Hu et al. 2004). As we mentioned above, in ovarian cancer, SLPI is over-expressed and is thought to have a carcinogenic function (Hough et al. 2001; Clauss et al. 2005; Devoogdt et al. 2009) independent of its antiprotease activity (Simpkins et al. 2008). However, in Lewis lung cancer cells, the pro-tumoral activity was shown to be dependent on its protease inhibitor activity (Devoogdt et al. 2003). Also, it was described that SLPI plasma levels were elevated in lung cancer patients (Zelvyte et al. 2004). More recently, low level of SLPI was detected in oral squamous cell carcinoma compared with normal oral epithelium (Wen et al. 2011). Moreover, a inverse correlation was also reported between SLPI and histological parameters associated with tumor progression (Wen et al. 2011). Interestingly, SLPI reduced the hepatic Lewis lung carcinoma metastasis (Wang et al. 2006). In breast tumors, the mRNA expression of SLPI either increases or decreases depending on the case (Kluger et al. 2004; Stoff-Khalili et al. 2005). Also in a breast tumor cell line, the SLPI overexpressing cells did not develop tumors in mice (Amiano et al. 2013). This effect was specific for this type of cell line, since colon tumor cells overexpressing SLPI, developed faster tumors than control cells. Moreover, the breast cancer cell line that overexpresses SLPI showed a decrease in E-cadherin expression, pro-apoptotic effects and cell cycle arrests. (Rosso et al. 2014). Interestingly, the administration of these SLPI transfected cells, which do not develop tumor in immunocompetent mice, inhibited the tumor growth and increased the survival of mice that were inoculated with mock transfected control cells. (Amiano et al. 2011).

In ovarian cancer SLPI inhibits cell growth through an apoptotic pathway (Nakamura et al. 2008), while, it has been also described that over-expression of SLPI is capable of producing a more aggressive ovarian cancer *in vitro* and *in vivo* models (Devoogdt et al. 2009). In fact, it was suggested that SLPI could be a useful diagnostic and prognostic tool in ovarian cancer (Carlson et al. 2013).

The SLPI gene and the protein expression are significantly lower in metastatic "head and neck squamous cell carcinoma" compared with non-metastatic ones. Also, an inverse significant correlation with HPV status was found for this kind of tumor (Hoffmann et al. 2013). Therefore, overall these data suggests us that it is not possible to generalize the findings related to SLPI expression and function in only a unique type of tumor, since its expression and modulation seems to be tumor specific.

Ischemia reperfusion injury

It has been described a protective effect of SLPI in different ischemia/reperfusion injury models, such as heart and liver (Amberger et al. 2002; Lentsch et al. 1999). We have also observed a beneficial effect of SLPI in kidney ischemia reperfusion injury (unpublished result). Interestingly, in cardiac transplantation, null mice for SLPI had an impaired function after cold ischemia unlike the wild type (Schneeberger et al. 2008). Moreover, when SLPI was added to the preservation solution, myocardial contraction was restored to normal.

Central Nervous System Ischemia

In two rat models, one of focal cerebral ischemia (Wang et al. 2003) and the other of spinal injury, it was observed high levels of SLPI. The same was seen in ischemic stroke in humans (Ilzecka et al. 2002). Interestingly, the administration of SLPI has been shown to be neuroprotective in both models of injury in rats (Wang et al. 2003; Hannila et al. 2013). Taking into account that the SLPI can promote axonal regeneration, plus the evidence of their neuroprotective effects, we could consider this molecule as potential therapeutic tool for different nervous system diseases (Hannila 2014).

Biomarker

It has been found that the determination of serum SLPI levels could be useful as a marker of several diseases, such as disease activity in systemic sclerosis with interstitial lung disease (Aozasa et al. 2012). Also, it has been suggested that a form of cleaved SLPI can reflect the disease activity of patients with allergic rhinitis and asthma (Belkowski et al. 2009). It was also been proposed as a biomarker in ovarian and gastric cancer (Devoogdt et al. 2009; Cheng et al. 2008), or to identify subjects at risk of infections and malignant transformation due to HIV infection (Nittayananta et al. 2013). Recently, it was proposed as a biomarker for acute kidney injury after transplantation (Wilflingseder et al. 2014). However, until now none of these assays have been introduced in the clinical settings.

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