

Secretory Leukocyte Protease Inhibitor and *Helicobacter pylori* in the Gastrointestinal Tract of HIV-infected Persons

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Citation

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Abstract

Prevalence/incidence of *Helicobacter pylori* (Hp) is reduced in HIV/AIDS. HIV-infection may alter the prevalence/incidence or pathology of *Helicobacter pylori* (Hp) infection. Secretory leukocyte protease inhibitor (SLPI) is an important broad spectrum innate immunity component that has anti-bacterial and HIV-1 inhibitory activity in different mucosal secretions and possibly in the local mucosal tissue milieu. Several human mucosal fluids contain SLPI which is an anti-microbial bio-molecule with anti-inflammatory and wound healing properties. SLPI plays an important role in gastric diseases. The underlying mechanisms should be clearly examined and elucidated. Reduced SLPI levels in the event of local infections are consistent with an increased risk of HIV infection. SLPI is produced in the gastrointestinal tract and may play an important role in Hp infection. We review the literature associated with SLPI and Hp to generate hypotheses and provide possible explanation for addressing the Hp prevalence/incidence issue in HIV/AIDS.

INTRODUCTION

Recently, Romanelli et al. discussed alteration of prevalence/incidence or pathology of *Helicobacter pylori* (Hp) infection [1] in HIV-infected persons. This is an important question because gastrointestinal (GI) complaints are common among HIV-infected persons and Hp infection is an important cause of GI problems. Therefore the authors suggested that “an increased incidence of Hp infection would contribute to the prevalence of GI complaints in the HIV-infected population.” [1] Although not enough hard-evidence exists about altered prevalence/ incidence of Hp infection in HIV-positive non-AIDS patients, the authors stated “it does appear that the incidence of Hp infection is lower among patients with AIDS compared to matched HIV-infected and –uninfected controls. [1] They suggested a greater number of well-designed and controlled trials to answer this question definitively. However, one key aspect of this issue – understanding the potential immunological mechanisms in response to Hp infection in GI system, especially the gastric mucosa is not clear. Is there an immunological mechanism at the mucosal level that may regulate Hp that has the potential to be altered in HIV infection?

It has been suggested that decreased susceptibility to Hp infection in HIV positive patients may not be explained by the abnormal reactivity of their humoral or cellular immune

response measured by antibody generation, [2] but reduced Hp colonization in HIV/AIDS [3] and reduced local inflammatory response has been noted in gastric antral biopsies. [4] HP works through release of cytokines, lipopolysaccharide, heat-shock protein enzymes etc. leading to inflammatory cascade initiated (cytokines, neutrophils, lymphocytes, etc.) and through hydrogen ion and pepsin release to damage gastric mucosa. [5] In the HIV-infected state, innate immunity offers among others, one possible explanation for the action of Hp in gastric ulcer disease through the putative action of Secretory Leukocyte Protease Inhibitor (SLPI).

SLPI is an important component of innate immunity that may be responsible for HIV-1 inhibitory activity in different mucosal secretions [6] and possibly in the local mucosal tissue milieu. Reduced SLPI levels in the event of local infections are consistent with an increased risk of HIV infection. [7] Because of the role of SLPI in innate mucosal defense in immunocompromised states has come to light through several studies, we believe that it may offer some insights into explaining the mechanisms associated with prevalence of Hp in HIV-infected persons that may be explored further in directed studies. In this paper, we review the role of SLPI in Hp-related gastric disease. Based on the evidence from current literature; we propose an explanation the apparently conflicting observations about SLPI

concentrations in gastric mucosa associated with Hp infection and suggest a scenario to explain reduced prevalence of Hp in HIV-infection. Through this discussion we hope to stimulate further research in this important area.

BRIEF REVIEW OF LITERATURE

SECRETORY LEUKOCYTE PROTEASE INHIBITOR

SLPI is a cationic 12 kDa serine antiprotease composed of two cysteine rich domains with a protease inhibitory site situated at leucine 72 in the carboxy-termination domain. [8] It was first described in seminal fluid, [9] and then also found in bronchial fluids, cervical fluids and saliva. [10] Subsequently, SLPI has been described in several body fluids. [6] Before being named SLPI, the molecule was known as anti-leukoprotease. Its role has been investigated in a variety of conditions – it has been found to be antibacterial, [11,12] antifungal, [13,14] anti-retroviral [15,16,17] and to have an important role in mucosal defense. [18,19] SLPI is one of the inhibitors that interfere with serine proteases. Being an anti-inflammatory molecule, [20,21] SLPI is found across wide variety of tissues. [21] It may facilitate tumor spread [20] and is helpful in wound healing. [10] Elevated SLPI in local fluids have been demonstrated in sepsis, [22] labor, [23] and sinusitis. [24] SLPI levels in saliva were found to correlate with history of oral candidiasis in HIV-1 positive patients. [25]

Epithelial cells participate in immune regulation and maintaining mucosal integrity by generating a range of important biologically active mediators [26] including SLPI. Autonomous keratinocyte cytokine, IL-1alpha, has recently been shown to up-regulate SLPI and increase expression of SLPI mRNA in a dose- and time-dependent manner. SLPI may modulate innate epithelial cell immunity in skin and mucosa, [27] and attenuate excessive inflammatory responses assuring balanced functioning of innate immunity. [28]

In its wound healing function, SLPI acts via proepithelin/epithelin to operate a switch at the interface between innate immunity and wound healing. Zhu et al. [29] demonstrated that supplying proepithelin corrects the wound-healing defect in SLPI null mice. In oral epithelial wound repair, examined in SLPI-null mice demonstrated decreased matrix deposition but matrix metalloproteinase (MMP) activity was enhanced. [30] In mucosa, SLPI is thought to act through protease/ protease-inhibitor balance. SLPI, found in a variety of secreted mucosal fluids, is a known inhibitor of serine

proteases such as neutrophil elastase, cathepsin G, mast cell chymase, and a chymotrypsin-like enzyme found in stratum corneum. [10,20,28]

The protease/ protease-inhibitor balance is critical for SLPI and is determined by a variety of factors and complex interactions between various cytokines and elafin, cathepsins, MMPs and elafin. Interferon-gamma stimulates MMPs, cathepsins, and other chemokines but inhibits SLPI. [31] SLPI is a substrate for membrane type 1-MMP in breast carcinoma cell cultures. [32] However, in lung disease, a somewhat different effect has been reported – that SLPI and elafin are resistant to proteolytic inactivation by MMP-8. [33] Cathepsin B serine proteinases may, however cleave and inactivate SLPI. [34,35] Earlier studies had reported that SLPI inhibits chymotrypsin, trypsin, elastase, and cathepsin G. [36]

SLPI IN GASTROINTESTINAL MUCOSA

Little is known about the potential endogenous anti-inflammatory molecules in the gastrointestinal tract (GIT). Research in the last few years has demonstrated that SLPI may play an important role in the GIT as a serine proteinase inhibitor, a potent antibiotic, a potential anti-inflammatory molecule and a potential wound healing promoter. SLPI may also prevent tissue injury that may result from excessive release of proteolytic enzymes by inflammatory cells. However, all GIT cells secreting SLPI have not been clearly established. Slowly, a body of research reports assessing the role of SLPI in different parts of GIT, under different disease states is building up. Most of the work has been done in relation to SLPI and Hp infection in gastric mucosa.

Natural anti-microbial peptides are increasingly recognized for their protective effects in mucosal surfaces. SLPI is the dominant protease inhibitor in the mucus secretions of the respiratory and genital tracts; is acid-stable, and could survive the acidic environment in the stomach and in the GIT can come from two possible sources. First, SLPI in saliva could be swallowed, and second, SLPI could be locally produced in the GIT. Locally produced SLPI could be sourced from exocrine glands or mucosal epithelial cells. Nystrom et al. studied the extent to which swallowed SLPI contributed to its actions in the GIT by assessing the turnover of swallowed SLPI in the gastrointestinal tract. [37] They reported that SLPI is rapidly degraded in the stomach and duodenum – they could not find any measurable amounts of SLPI in the feces.

Distribution of SLPI in the gastric mucosa varies according

to anatomical location of mucosa in the stomach. Gastric epithelial SLPI concentration is reported to be higher in the antrum than in the body of the stomach. [38] In another study to find out whether SLPI is actually secreted from normal human colonic mucosa, Nystrom et al. examined the biopsy area and circumference of punch biopsies (3,4, and 6 mm diameter) of cancerous as well normal colonic mucosa taken from thirty six patients with colonic cancer. [39] They reported that all samples contained SLPI at varying concentrations and that SLPI secretion seemed dependent on the circumference of the biopsy rather than on the area of the biopsy. [39] SLPI levels in corpus and duodenal mucosa are not affected by low-dose aspirin. Although the design of these studies [38,40] were questionable in that the age group of subjects investigated and aspirin doses were markedly different, unless there is reason to suspect that there occurs differential suppression of SLPI according to age and aspirin dose, the general conclusion that SLPI levels were independently lower in gastric mucosa only in the antrum [40] and not other locations would be valid.

In the small intestine, SLPI has been demonstrated in the Paneth cells and in scattered mucosal goblet cells. In normal mucosa of the large bowel, SLPI has been demonstrated in the scattered goblet cells in the epithelium. In addition, immunoreactive SLPI was frequently found in colonic adenomas. [41] Using reverse-transcriptase polymerase chain reaction (RT-PCR), si-Tahar et al., demonstrated SLPI mRNA in human model intestinal epithelial cell lines (such as Caco2-BBE, T84, and HT29-Cl.19A) in human jejunum and in colon biopsy specimens. [42] Their report suggested that the constitutive secretion of SLPI occurs in a markedly polarized manner – toward the apical surface and is enhanced by inflammatory mediators including TNF- α and IL1- β which were increased to about 3.5 times of the control value. They further demonstrated SLPI protein in intestinal lavage fluids collected from normal adult humans and that recombinant SLPI attenuates trypsin- or elastase- induced permeability alteration of epithelia in a dose-dependent manner but it did not influence transepithelial conductance measurements or electrogenic ion transport across epithelium. [42]

SLPI AND HP

Concentration of SLPI in gastric mucosa is reduced markedly in Hp-infected patients taking aspirin. [38] SLPI concentration is generally induced during inflammation; however Hp infection may influence protease/ protease-

inhibitor balance in the gastric mucosa [43] in a way that Hp infection down-regulates gastric antral SLPI levels. [36] Wex et al. demonstrated that SLPI levels were lower in Hp-induced inflammation in gastric mucosa only in the antrum. [40] Hp-mediated gastritis is associated with significantly decreased antral SLPI levels – in 2004, Wex et al. reported that subjects infected with Hp exhibited a strong decline in SLPI levels in gastric antrum compared to Hp-negative subjects and those infected with Hp previously from whom the bacteria had been eradicated. [44] Furthermore, this reduction in SLPI levels was specific for the gastric antrum – antral SLPI level was inversely correlated with inflammatory scores of antrum-predominant gastritis. [44]

SLPI REGULATION IN GASTRIC MUCOSA

The down-regulation of SLPI [45] occurs at translational or posttranslational level and is completely reversed after Hp-eradication therapy. Wex et al. [45] analyzed mucosal SLPI concentration in patients with non-ulcer gastric dysplasia, duodenal ulcer, and gastric adenocarcinoma. They found that gastric antral SLPI levels were reduced in Hp-infected patients in all the three groups by 75% compared to those who did not have Hp infection. Furthermore, gastric tumor tissue SLPI levels were twice that of the surrounding tumor-free mucosa. Although the SLPI levels of gastric adenocarcinoma were lower than that of Hp-negative patients, the reported results were not statistically significantly different. They tested for and did not find SLPI transcript levels to be different between the groups and mucosa locations and therefore suggested that transcriptional regulation of SLPI was not an involved regulatory mechanism. It is likely that local down-regulation of SLPI in antral mucosa is a general phenomenon of Hp-related diseases. [45] Down-regulation of SLPI was confirmed by another study by the same research group. [46] This latter study substantiated the observation that SLPI antagonizes neutrophil elastase by reporting negative correlation between SLPI levels in antral biopsies of Hp-positive subjects and activity of neutrophil elastase. They found a 30-fold increase in neutrophil elastase activity with lower SLPI. Over time, however, eradication of Hp resulted in restoration of SLPI level. Wex et al. suggested that Hp-induced decrease in SLPI is primarily regulated at the posttranslational level. [47]

As a consequence of above reports, a natural question about SLPI regulation would be: is the downregulation of SLPI in gastric mucosa a specific response to Hp infection – or more generally linked to gastric inflammation? Addressing this

question, Hirtz et al. reported that SLPI response was specific, and not general in nature. [47] In comparison with the control group, the SLPI expression of antral mucosa in Hp-mediated- and lymphocytic- gastritis was significantly lower. However, epithelial SLPI expression was not affected in NSAID-enhanced and autoimmune gastritis either in the antrum or corpus, respectively. Both types of gastritis revealed a significantly lower expression of SLPI in infiltrating immune cells, whereas those immune cells infiltrating the corpus in autoimmune gastritis exhibited higher SLPI levels than the immune cells of all other groups in the reported study. [47]

DISCUSSION

Hp drills into the mucus gel layer of the stomach, produces adhesins to help its binding to epithelial cells and produces proteases, catalases, and phospholipases which damage epithelial cells. Hp also produces urease that metabolizes urea (producing ammonia and carbon dioxide) which neutralizes gastric acid. The ammonia that is produced is toxic to the epithelial cells. SLPI has the capacity to neutralize Hp-proteases. Recently, strong down-regulation of SLPI was identified in the antral mucosa of Hp-infected subjects. This Hp-infection-specific decrease [47] was inversely associated with the degree of gastritis, [44] and was confirmed in other studies [40,41,42,43,44,45,46,47]. These observations from clinical studies were confirmed in-vitro using four gastric tumor cell lines after – co-incubation of these cell lines with Hp resulted in lower or unchanged SLPI protein levels, the corresponding SLPI mRNA amounts were upregulated by up to five-fold in all cell lines. [45] SLPI gene was identified as a target gene in Hp infection and in patients with Hp -related disorders. [45,46,47]

In HIV-infection, where cell-mediated immunity is compromised, epithelial surface non-specific innate immunity mechanisms such as those involving SLPI may assume greater importance in protection of epithelial integrity in the face of Hp-challenge. In HIV-uninfected gastric mucosa, post-translational regulation of SLPI vis-à-vis Hp infection and the rebound phenomenon after eradication may be explained by SLPI balance in the local milieu. Normally there would be a resident level of optimal SLPI in gastric mucosa. Exposure to Hp released proteases will neutralize SLPI which would then lead to a reactive upregulation of local SLPI production (i.e. upregulation of SLPI mRNA [45]). It is intuitive to expect a dose-response association between Hp protease challenge and epithelial

SLPI production. As long as SLPI production keeps pace with depletion, this protease/ protease-inhibitor balance would be maintained. However, once the biological threshold (maximum rate) for SLPI production is reached, any further increase in protease challenge would lead to net SLPI depletion in the local milieu. The net SLPI production would be further challenged as Hp infection (and other existing co-factors) starts to damage the epithelial cells (reduction in number of SLPI producing cells). During post-Hp-eradication recovery, as the epithelium builds up, there would be an apparent “upregulation” of SLPI because the SLPI produced would not be used up as rapidly. Thereafter, as the critical mass of epithelial cells is restored, SLPI balance of the local milieu would be restored to normal homeostasis.

In HIV/AIDS, CD4+ cells in local mucosal milieu are depleted. From assessment of statistical models in a study of oral candidiasis and SLPI in HIV-infected persons, it has been suggested that CD4+ cell depletion may lead to an upregulation of SLPI in the oral cavity. [25] Although this hypothesis has not been tested experimentally, it is supported by the observation of upregulation of SLPI mRNA in keratinocytes mediated by IL-1 alpha. [27] If found to be true in-vivo, it may provide insights into SLPI response in HIV – Hp co-infection in gastric mucosa i.e. then HIV-induced SLPI production could explain reduced Hp prevalence in HIV-infected states because HIV induced reduction in mucosal CD4+ cells would up-regulate SLPI which in turn would control Hp in gastric mucosa. This could occur because SLPI, by neutralizing Hp proteases would help maintain epithelial integrity and allow other mechanisms to control Hp before it can induce much epithelial damage or find its ecological habitat in the gastric mucosa. It has been suggested that CD4+ T cells are involved in anti Hp immune response and that Th1 cells play an important role in peptic ulcer pathogenesis. [48] Furthermore, Hp-specific memory CD4+ T cells may be suppressed in Hp infection. [49] Therefore, the role of non-specific innate immunity in combating Hp in HIV/AIDS would be very important.

Role of epithelial cells in HP-infection host defence is currently being thought to be more fundamentally important than considered earlier. [50] It has been suggested that in addition to specific bacterium-host cell interactions, molecular cross-talk between different cell populations may contribute to innate immune signaling to Hp in which

epithelial cells and lymphoid cells may be involved, [50] in the process leading to increase in pathogen recognition molecules in the local mucosal milieu. It has been suggested that it is the GIT and not the peripheral lymphoid tissue that is the initial site for HIV-disease. [51] The GIT mucosa CD4+ T cells are quickly depleted within 7-14 days of infection, primarily from the lamina propria of GIT and this depletion precedes CD4+ T cell depletion in the blood. [52] Therefore with lack of Hp-specific memory T-cells [49] in HIV/AIDS it is likely that innate immunity factors play a more important role in controlling Hp-infection. Because SLPI-Hp interaction mechanisms have been experimentally demonstrated in gastric mucosa, and SLPI has been demonstrated to be an important innate immunity component in HIV-associated infections, we consider that it is likely that SLPI may play an important role in Hp-prevalence in HIV/AIDS GIT.

Hp-specific response of SLPI in GIT mucosa has not been fully understood although a series of complex immune mechanisms have been demonstrated to be active during initial infection and persistence of the organism in GIT. [53] Among the several aspects of Hp-infection that need further examination one aspect is the genetic variation and phase-changes in Hp clonality that have been reported to occur. Whereas different Hp-variants may infect different people, it has generally been assumed that Hp-clonality is maintained within an individual person (and across time in the same person). However, it has also been demonstrated that “within an apparently homogeneous population, as determined by macro-scale comparison and nucleotide sequence analysis, remarkable genetic differences exist among single-colony isolates” of Hp. [54] It may be possible that Hp-clonality changes occur in different phases of HIV/AIDS and a different variant of Hp may predominate at different times. If clonal selection occurs in gastric mucosa (as a function of CD4+ memory T-cell activity), then it may be possible that in HIV/AIDS several Hp-strains may compete and those which are more susceptible to non-specific innate immunity may predominate, leading to their eventual easy removal.

At the same time, Hp-incidence in HIV/AIDS may simply be a function of state of the gastric mucosa wherein the initial HIV-infection removes Hp-memory T cells leading to a rapid epithelial destruction in the face of reasonable/ large Hp-challenge, thereby removing the ecological niche of Hp. In such situations, low prevalence of Hp in HIV/AIDS would be a direct result of the resultant atrophic gastric

mucosa. However, atrophic gastritis is not a commonly reported condition in HIV/AIDS.

In HIV-uninfected states, the immune mechanisms associated with Hp-infection are not fully understood, and very little research has been conducted in HIV-Hp infection. We attempted to explain some of the observations using SLPI as a possible player in prevalence of Hp in HIV/AIDS. However, SLPI is only one of the several components of innate immunity, although it may play a significant role in Hp-control in HIV/AIDS, but much further research needs to be done to answer the question of Hp prevalence/ incidence in HIV/AIDS and involved mechanisms. Furthermore, if the role of SLPI is found to be significant, it may be possible to assess SLPI levels/ SLPI gene up-/ down-regulation as potential marker for progression of/ recovery from Hp-infection. If the role of SLPI in gastric disease is found to be substantial, it may also be possible to think of using recombinant SLPI supplement in the form a drink to control Hp-induced gastric diseases.

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