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ROLE OF SALIVARY SECRETORY LEUKOCYTE PROTEASE INHIBITOR IN HIV: A REVIEW

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ABSTRACT

Saliva is a promising option for diagnosing certain disorders and monitoring the evolution of certain pathologies or the dosage of medicines or drugs. Its advantages as a diagnostic tool include its being easy to obtain and the positive correlation between many parameters in serum and saliva. Saliva plays an essential rôle in maintaining the integrity of the oral structures, in personal relationships, in the digestion and in controlling oral infection.

Human secretory leukocyte protease inhibitor is a cationic protein in saliva has been found to be the most potent anti-HIV-1 factor among several innate inhibitory molecules namely, virus-specific antibodies, mucins, and thrombospondins, identified and purified from saliva. This review includes the role of slpi as a anti HIV factor, there by reducing the risk of oral transmission of HIV and also antiprotease, bactericidal and antifungal activity are also discussed.

Keywords: saliva.HIV, SLPI

INTRODUCTION

Human immunodeficiency virus transmission from oral secretions of the millions of HIV affected individuals during, dental treatment, biting and aerosolization is a rare event even when infectious HIV is shed into the oral cavity by infected blood or exudates. Despite its shedding of infected blood or exudate, saliva of infected individuals usually contains only non-infectious components of HIV indicating that there may be a break down or inactivation of infectious HIV and may contain fragments or the entire non-infectious genome Human secretory leukocyte protease inhibitor is a cationic protein in saliva has been found to be the most potent anti-HIV-1 factor.[2,3,4.]

Human secretory leukocyte protease inhibitor (SLPI) is an 11.7-kDa cationic protein which plays a vital role in innate immunity. It is a non glycosylated, highly basic, acid-stable, cysteine-rich, 107-amino acid single-chain polypeptide

Antiprotease and anti-inflammatory activities:

SLPI exerts its antiprotease activity by stabilizing the protease-antiprotease complex and may mediate the enhancement by heparin. The balance between proteinases and antiproteinases is a prerequisite for the maintenance of tissue integrity. The cleavage of SLPI results in increased tissue damage. SLPI also shields the tissues against inflammatory products by down-regulating the macrophage responses against bacterial

lipopolysaccharides(LPS). LPS directly induce SLPI production by macrophages or by way of interleukin-1β (IL-1β), tumor necrosis factor alpha, IL-6 and IL-10. SLPI renders macrophages, thus inhibits release of proinflammatory cytokines and nitric oxide. SLPI along with other factors manifests its anti-inflammatory profile by decreasing the C5a-related chemotactic activity. Thus, the accumulation of SLPI in the local tissue environment may represent an intrinsic feedback inhibition mechanism**.**

Bactericidal and antifungal activities

SLPI has broad-spectrum antibiotic activity that includes bactericidal and antifungal properties. The mechanism of the SLPI- mediated bactericidal activity includes binding of the protease inhibitor to the bacterial mRNA and DNA.

SLPI has fungicidal activity against human isolates of the pathogenic fungi Aspergillums fumigatus and Candida albicans by partial inhibition of fungal protease activity as it has been demonstrated using recombinant SLPI (rSLPI).

The antibacterial and antifungal activities are related to the cationic nature of SLPI, thus SLPI may provide a valuable therapeutic option in the future treatment or prevention of infectious diseases.[2,3,4]

Role of Oral Environment in HIV Transmission:

During the asymptomatic infection HIV shed at any mucosal surface originates from infected mononuclear leukocytes. The cell free infectious HIV has low infectivity for the CD4 negative epithelial cells on all mucosal surfaces.

In saliva, inhibition of HIV may be partly due to several inhibitors of viruses that are present in saliva. Free secretory antibody also is present in saliva but may not be effective due to its low concentrations.

Since most of the infectious virus that is shed orally during the asymptomatic phase of infection, it is hypothesized that saliva may disrupt these infected cells and render them incapable of supporting virus multiplication and cell to cell transmission of HIV.[3,4]

For long time researchers in dental profession were deeply interested in the study of saliva to be used as a diagnostic tool for various oral as well as systemic diseases. Despite the low frequency of isolation of HIV in the saliva, a high frequency of salivary antibodies to HIV are observed. This opened a reliable and easy screening approach for HIV / AIDS.

SLPI was first isolated from secretions of patients with chronic obstructive pulmonary disease and cystic fibrosis and was thereby considered a major antielastase inhibitor. SLPI is produced by neutrophils, macrophages, beta-cells of pancreatic islets, epithelial cells investing the renal tubules, acinar cells of parotid and submandibular glands, acinar cells of submucosal glands, and epithelial cells lining mucous membranes of respiratory and alimentary tract. SLPI was originally isolated from parotid saliva and has been detected in a variety of secretions such as whole saliva, seminal fluid, cervical mucus, synovial fluid, breast milk, tears and cerebral spinal fluid. SLPI was found to play a pivotal role in apoptosis and wound healing. SLPI has alternative names called mucus protease inhibitor, anti leukoprotease, bronchial secretory inhibitor, human seminal inhibitor I, cervix uteri secretion inhibitor, and secretory leukoprotease inhibitor. The physiologic concentration of SLPI in saliva is 0.1 to 10µg/ml.[2, 3]

ROLE OF SLPI IN HIV:

SLPI is likely to be a major deterrent of immunodeficiency varies type-1(HIV-1) transmission through oral secretions. There are evidences suggesting that mucosa account for the most easily accessed route of HIV-1

transmission, paradoxically, the oral cavity is a rare route of transmission. SLPI was found to be the most potent anti-HIV-1 factor among several innate inhibitory molecules namely, virus-specific antibodies, mucins, and thrombospondins, identified and purified from saliva. Moderate activity is also exerted against HIV-2 strains, but only when the concentration of SLPI exceeds the norm.

The mechanism by which SLPI inhibits HIV-1 infection is still elusive, but it appears to involve the host cell target rather than binding to the virus. Moreover, SLPI's antiviral activity appears to be distinct from its known antiprotease activity. Evidence suggests that SLPI blocks HIV-1 internalization in a dose-dependent manner rather than binding to CD4 and inhibits a step of viral infection that occurs after virus binding but before reverse transcription. SLPI confers local protection against microbial, fungal, and HIV-1 insults. It is noted that among proteins present in the saliva, only SLPI has anti-HIV-1 activity at physiological concentrations.[4,5,6,7]

Studies have shown that defensins reduce the lytic action of human. Defensins are important mediators of the innate defense of mucosal against microbial infections. Several α defensins and microdefensins are effective inhibitors of HIV-1 infection in vitro, and recent evidence implicates α defensins in resistance to HIV-1 progression in vivo.[7]

Some studies revealed that HIV-1 induces expression of β- defensins on human oral epithelial cells and block HIV replication by direct interaction with the virions by modulation of the C and CR4 co receptor. [8]

Qualitative and quantitative tests for HIV patients to detect free HIV in saliva concluded that HIV was present in low level even in the presence of severe periodontal disease. This is probably due to the low levels of mononuclear cells in salivary glands and gingiva and inhibitory factors in saliva of HIV infected patients[..9]

Saliva of seronegative individuals also has protective properties against HIV infectivity indicating that other non-immunological factors are involved in the HIV inhibitory capacity of saliva, including salivary proteins. [10].

The infection of primary monocytes with HIV-1 is significantly suppressed in the presence of human saliva. Human saliva blocked the infectivity of HIV-1 by inverse transcriptase for 3 weeks after an hour exposure of monocytes to the virus, whereas other human fluids failed to reduce the infectivity of virus.[11]

Research conducted has identified a salivary protein that reduces HIV infectivity by thrombospondin 1(TSP-1) that adheres to HIV surface protein gp120 and strongly inhibits the ability of the virus to enter peripheral blood mononuclear cells invitro.[12]

According to some studies lysosome proteins, when present above physiological levels, act jointly to attack HIV with lysozymes destroying viral membranes while ribonucleases block reproduction of the virus by destroying its genetic material.[13]

Lactoferrin secreted by neutrophils and exocrine glands, is found in saliva, breast milk, tears, semen and other mucosal secretions. It can inhibit HIV replication both when iron saturated and when not, and it can also interfere with the adhesion and entry of HIV to host cells. [14]

Hypotonic saliva inhibits the production of HIV by infected leucocytes which contributes to the extremely low oral transmission. Salivary hypo toxicity appears to destroy the cell wall of HIV infected mononuclear leucocytes, preventing them from binding to mucosal epithelial cells and producing infective HIV.[15]

Recent studies demonstrated that basic proline rich proteins found in human parotid saliva have a potent anti HIV-1 activity independent of that attributed to SLPI and TSP-1. Its action

mechanism is based on the binding of these proteins to the gp120 of the virus, preventing entry of HIV into the host cell.[16]

Salivary antibodies against HIV were identified at the beginning of the HIV pandemic. It appears that HIV infection is associated with decreased, salivary IgA levels, although a dichotomy has been reported between IgA concentrations in saliva and serum. Thus the presence of specific anti- HIV antibodies (IgA, IgG, and IgM) can be readily detected in saliva of seropositive patients but at a much lower level than in blood.[17]

Various studies conducted on inhibitors of HIV encoded protease combined with nucleoside analogues with antiretroviral activity, cause profound and sustained suppression of viral replication thereby reducing morbidity and prolonging life in patients with HIV infections. The 4 approved HIV protease inhibitors are based on amino acid sequences recognized and cleared in HIV proteins.[1] Association of SLPI levels with reduced transmission of HIV 1 studied in breast milk, concluded that higher SLPI levels protect the infant against HIV-I infection after exposure to HIV-1 through breast milk.[19]

Studies conducted have revealed that hypotonic disruption may be a major mechanism by which saliva kills infected mononuclear leukocytes, it prevents their attachment to mucosal epithelial cells and production of infectious HIV there by preventing transmission.[20]

Some studies demonstrated that recombinant human secretory leukocyte protease inhibitor inhibits infection of lymphocytes and monocyte derived tumor cell lines and peripheral blood lymphocytes with laboratory adapted isolates and with the primary isolate, NDK of free human, (HIV-1). In contrast, rhSLPI did not inhibit inhibitory activity toward transcytosis of cell associated HIV-1 through a light monolayer of endometrial epithelial cells. They concluded that inhibitory effect of SLPI is restricted to free HIV-1 in corporal fluids.[22]

According to one in vitro study, SLPI contribute to the anti HIV-I activity of human saliva. Thus it may play an important role in the unique HIV-1 infectivity activity of human saliva and SLPI is generally present at higher concentrations in tissues associated with lower rates of transmission of HIV-1. If an inverse correlation exists between levels of SLPI and the risk or rate of HIV-1 transmission, exogenously administered SLPI may afford protection against this lethal virus.[23]

A study was carried out to compare the inhibitory capacity of saliva from the 4 major types of salivary glands separately, suggesting the neutralizing capacity of glandular saliva towards HIV-IIIB strain and glandular saliva's interfering at different sites during the virus replication cycle.[24]

According to some authors inhibition of HIV may be partly due to presence of inhibitors of viruses that are present in saliva and hypothesized that most of the infectious virus that is shed orally during the asymptomatic phase of infection is produced by infected leucocytes. The CD4 negative mucosal epithelial cells resist infection by cell free HIV, disrupt these infected cells and thus render them incapable of supporting virus multiplication and cell to cell transmission of HIV.[24] An in vitro study to know the effect of increasing concentration of humanL1 acid glycoprotein on anti viral activity in AIDS patients was carried and assessed experimentally in vitro anti HIV activity.[25]

Studies on anti leukoprotease suggested that endogenous protease inhibitors may participate in mucosal host defense. They reported in the antimicrobial activity of recombinent (V) AGP toward the human fungal pathogens Aspergirus Fumigatus, and Candida Albicans or ALP expressed pronounced fungicidal activity toward

metabolically active a yeast cells of these fungus[26]

A study was conducted to asses SLPI in HIV infection on 65 HIV seropositive patients which revealed that SLPI inhibits HIV-1 infection of human monocytes at physiological concentration by its inhibitory effect by blocking HIV binding to host cells. SLPI is an antimicrobial protein found in saliva SLPI is secreated by the serous acinar cells of parotid and van-abner glands. SLPI has broad antimicriobial activity and has been shown to inhibit candidal and viral growth.[27]

Researchers from Atlanta found that saliva contains two inhibitory components one particulate and the other remaining in the filtrate. Inhibition of virus infectivity by saliva was not due to low pH or due to other constituents such as lysosomes, lactoferrin and lactoperoxidase. Also the fact that anti-HIV IgA antibodies are present in saliva of infected persons, may contribute to the low frequency with which HIV has been recovered from saliva of infected persons and the apparent lack of oral transmission of the virus.[28]

CONCLUSION

The present review suggests a multifaceted role for SLPI. This SLPI has been found to be the most potent anti-HIV factor among several innate inhibitory molecules; it can be used as an adjunct to various diagnostic procedures implied for the risk of oral transmission of HIV infection .Finally SLPI is used as a marker to monitor the progress of an infection or a malignant lesion.

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