Primljen/ Received on: 04.04.2019
Revidiran / Revised on: 12.04.2019
Prihvaćen/ Accepted on :25.05.2019

INFORMATIVNI RAD
INFORMATIVE ARTICLE
doi: 10.5937/asn1979936A

SEKRETORNI LEUKOCITNI INHIBITOR PROTEAZE I NJEGOVA ULOGA U NASTANKU KARCINOMA GLAVE I VRATA

SECRETORY LEUKOCYTE PROTEASE INHIBITOR AND ITS ROLE IN VIRUS INDUCED HEAD AND NECK CANCERS

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Sažetak

Uvod: *Oralni karcinom skvamoznih ćelija (OSCC) je najčešći zloćudni tumor i čini preko 90% oralnih karcinoma. Iako je konzumiranje duvana u raznim oblicima glavni etiološki agens, danas je učestalost karcinoma izazvanih virusom u porastu.*
Humani sekretorni inhibitor leukocitne proteaze (SLPI) je član (urođenih) proteina povezanih sa imunitetom. Ima raznovrsna dejstva uključujući antiinflamatorno, antibakterijsko, antifungalno i antivirusno. SLPI je identifikovan kao jedini najsnažniji faktor u sprečavanju prenosa HIV-1 kroz oralnu sekreciju. Studije su nedavno pokazale njegov efekat protiv virusom izazvanih oralnih karcinoma. Najčešće proučavani virusi u oralnoj onkogenezi uključuju Humani Papilloma virus, Epstein Barr virus i Herpes simplex virus. SLPI je pokazao inverznu korelaciju sa pojavom HPV-pozitivnih tumora. U prisustvu HSV infekcije postoji smanjena regulacija SLPI. Smanjen SLPI je zabeležen u Epstein Barr virus povezanom nazofaringealnom karcinomu. Ovaj informativnii članak razmatra različite efekte SLPI sa posebnim fokusom na njegove efekte na virus humane imunodeficijencije-HIV, Humani Papilloma virus, Herpes simplex virus i Epstein Barr virus.
Zaključak: *Povećana SLPI ima zaštitnu ulogu u virusnoj onkogenezi, dok smanjeni nivoi povećavaju verovatnoću virusne infekcije.*

Ključne reči: *sekretorni inhibitor leukocitne proteaze, Humani Papilloma virus, Epstein Barr virus, Herpes simplex virus, oralni karcinom*

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Abstract

Introduction: *Oral squamous cell carcinoma (OSCC) is the commonest oral malignancy and accounts for over 90% of oral cancers. Though tobacco consumption in its various forms is the main etiological agent, nowadays, the incidence of virus induced cancers is increasing.*
Human Secretory Leukocyte Protease Inhibitor (SLPI) is a member of the innate immunity-associated proteins. It has a variety of actions including anti-inflammatory, antibacterial antifungal and antiviral effects. SLPI has been identified as the single most potent factor in preventing the transmission of HIV-1 through oral secretions. Studies have recently demonstrated an effect against virus induced oral cancers. The most commonly studied viruses in oral oncogenesis include Human Papilloma Virus, Epstein Barr Virus and Herpes simplex virus. SLPI has shown an inverse correlation with the occurrence of HPV-positive tumours. In the presence of HSV infection, there is a down regulation of SLPI. Decreased SLPI has been noted in Epstein Barr Virus associated nasopharyngeal carcinoma. The present review discusses the diverse effects of SLPI with special focus on its effects on Human Immunodeficiency Virus, Human Papilloma Virus, Herpes Simplex Virus and Epstein Barr Virus.
Conclusion: *Increased SLPI has a protective role in viral oncogenesis while decreased levels increase the probability of viral infection.*

Key words: *Secretory leukocyte protease inhibitor, Human Papilloma Virus, Epstein Barr virus, Herpes simplex virus, Oral cancer*

Uvod

Oralni karcinom skvamoznih ćelija (OSCC) je najčešći zloćudni tumor i čini preko 90% oralnih karcinoma[1]. Ima multifaktorijallnu etiologiju sa genetskim i ekološkim faktorima koji igraju ulogu u njegovom nastanku. Iako je konzumiranje duvana u raznim oblicima glavni etiološki agens, danas je učestalost karcinoma izazvanih virusom u porastu[1]. Najčešće proučavani virusi u oralnoj onkogenezi uključuju *Humani Papilloma virus, Epstein Barr virus i Herpes simplex virus*[1].

Humani sekretorni inhibitor leukocitne proteaze (SLPI) je katjonski protein povezan sa urođenim imunitetom. Gen SLPI je lokalizovan na hromozomu 20q12-13.2[2]. Ima različite imunološke sposobnosti koje uključuju njegovu antiinflamatornu i antimikrobnu aktivnost[3]. Zbog svoje antiproteazne aktivnosti, može inhibirati virusne infekcije[4]. SLPI je takođe proučavan kod mnogih vrsta karcinoma kao što su rak pluća, dojke, jajnika, jetre, itd. Ima ulogu u metastaziranju tumora[5]. Ovaj informativni članak se bavi različitim funkcijama SLPI i njegovom mogućom ulogom u karcinomima usne duplje izazvanih virusima.

Humani sekretorni inhibitor leukocitne proteaze (SLPI)

SLPI je prvi put identifikovan u sekretima pacijenata sa hroničnom opstruktivnom plućnom bolešću (COPD) i cističnom fibrozom pa se smatra inhibitorom antielastaze[2]. Nastaje iz različitih ćelija tela, uključujući neutrofile, makrofage, β-ćelije pankreasa, epitel bubrežnih tubula, acinusne ćelije velikih pljuvačnih i submukoznih žlezda kao i sluzokožu respiratornog i gastro-intestinalnog trakta[2,3]. U usnoj duplji je prvi put identifikovan u parotidnim sekretima, ali je od tada izolovan iz gotovo svih humanih izlučevina uključujući semenu, cervikalnu, cerebrospinalnu, sinovijalnu, nazalnu, bronhijalnu kao i iz majčinog mleka i suza[2,3].

Introduction

Oral squamous cell carcinoma (OSCC) is the commonest oral malignancy and accounts for over 90% of oral cancers[1]. It has a multifactorial etiology with genetic and environmental factors playing a role. Though tobacco consumption in its various forms is the main etiological agent, nowadays, the incidence of virus induced cancers is increasing[1]. The most commonly studied viruses in oral oncogenesis include *Human Papilloma Virus, Epstein Barr virus and Herpes simplex virus*[1].

Human Secretory leukocyte protease inhibitor (SLPI) is a cationic protein associated with innate immunity. The SLPI gene is localized on chromosome 20q12-13.2[2]. It has a variety of immunological capabilities, which include its anti-inflammatory and anti-microbial activity[3]. Due to its anti-protease activity, it can inhibit viral infections[4]. SLPI has also been studied in many cancers such as lung, breast, ovary, liver, etc. It has a role in metastasis of tumours[5]. The present review focuses on the various functions of SLPI and its possible role in virus-induced cancers of the oral cavity.

Secretory leukocyte protease inhibitor

SLPI was first identified in secretions from patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis and was considered as an antielastase inhibitor[2]. It is produced from varied cells of the body including neutrophils, macrophages, β-cells of the pancreas, epithelium of renal tubules, acinar cells of major salivary and submucosal glands as well as mucous membranes of respiratory and gastrointestinal tracts[2,3]. In the oral cavity, it was first identified in parotid secretions but since then has been isolated from almost all human secretions including seminal, cervical, cere-brospinal, synovial, nasal, bronchial as well as from breast milk and tears[2,3].

Antiinflamatorno dejstvo

Toksični proizvodi, kao što su serinske proteaze, koje oslobađaju neutrofili tokom inflamatornog procesa, uzrokuju veliko oštećenje tkiva . SLPI štiti tkivo od štetnih efekata upale uglavnom kroz njegovo delovanje na neutrofilnu elastazu. Deluje na makrofage i smanjuje oslobađanje infla-matornih citokina i azotnog oksida[2]. Uočeno je da gubitak SLPI dovodi do povećanog oštećenja tkiva . Takođe, inhibira i hemotaksu povezanu sa C5a.

Zarastanje rana

Utvrđeno je da se SLPI povećava kao odgovor na oštećenje kože. Smanjeni SLPI je povezan sa produženim vremenom zarastanja. Ova funkcija SLPI u promovisanju zarastanja rana je verovatno posledica njegove anti-inflamatorne aktivnosti koja dovodi do brže formacije matriksa u ranama[3,6].

Antibiotsko dejstvo

Studije su pokazale da SLPI može imati antibakterijska i antifungalna svojstva. To je baktericidno dejstvo protiv Gram-pozitivnih organizama kao što je *S. aureus* i Gram-negativnih organizama, kao što je *E. coli.* Ova baktericidna aktivnost može biti posledica vezivanja SLPI za mRNA ili DNK bakterije. Pored toga, može inhibirati razaranje opsonina i receptora za fagocitozu. On, takođe, može modifikovati obradu antimikrobnih peptida kao što su katelicidini[2,7].

SLPI je fungicidan za patogene gljive kao što su *Aspergillus fumigatus i Candida albicans.* Povećani nivo SLPI salivarnih ćelija produkuje se kao odgovor na oralnu kandidozu kod osoba zaraženih HIV-om. Koncentracije salivarnih SLPI smanjuju se sa godinama, koje mogu biti uzrok povećanih oralnih glji - vičnih infekcija kod starijih osoba [2].

Antivirusno dejstvo

Pošto mnogi virusi zahtevaju aktivnost proteaze za izazivanje infekcije, anti-proteaza, kao što je SLPI, može inhibirati virusne infekcije kao što je HIV. Ova anti-HIV aktivnost je nezavisna od njegove anti-proteazne aktivnosti. SLPI inhibira interakciju HIV-a sa receptorom na površini ćelije koji je identifikovan kao Aneksin 2[4].

Anti inflammatory Effects

Toxic products such as serine proteases which are released by neutrophils during the inflammatory process cause extensive tissue damage. SLPI protects tissue against the detrimental effects of inflammation mainly through its action on neutrophil elastase. It acts on macrophages and decreases the release of inflammatory cytokines and nitric oxide[2]. It has been seen that loss of SLPI results in increased damage to body tissues. Further, it inhibits C5a related chemotaxis.

Wound Healing

It was found that SLPI increased in response to cutaneous damage. The decreased SLPI was associated with the increased time of healing. This function of SLPI in promoting wound healing is probably a consequence of its anti-inflammatory activity leading to faster matrix formation in wounds[3,6].

Antibiotic Activity

Studies have postulated that SLPI may have antibacterial and antifungal properties. It is bactericidal against Gram-positive organisms such as S. *aureus* and Gram-negative organisms such as E. *coli*. This bactericidal activity may be due to binding of SLPI to mRNA or DNA of the bacteria. In addition, it may inhibit the destruction of opsonins and receptors for phagocytosis. It may also modify the processing of antimicrobial peptides such as cathelicidins[2,7].

SLPI is fungicidal to pathogenic fungi such as *Aspergillus fumigatus and Candida albicans.* Increased salivary SLPI levels are produced in response to oral candidiasis in HIV-1 infected persons. Salivary SLPI concentrations diminish with age which may be the cause for increased oral fungal infections in older individuals[2].

Anti-Viral activity

Since many viruses require protease activity for causing infection, an antiprotease like SLPI can inhibit viral infections such as HIV. This anti HIV activity is independent of its antiprotease action. SLPI inhibits the interaction of HIV with a cell surface receptor identified as Annexin 2[4].

SLPI je najefikasniji anti-HIV-1 faktor među urođenim inhibitornim molekulima u pljuvački[4]. Veruje se da inhibira transmisiju HIV-1 putem oralnog sekreta.

McNeeli je 1995. godine pokazao da je HIV-1 infekcija u monocitima blokirana humanom pljuvačkom[2,8]. SLPI je bio jedini molekul u pljuvački koji je imao antiretrovirusnu aktivnost u fiziološkim koncentracijama[9]. Ova anti-HIV-1 aktivnost SLPI je takođe viđena u perifernim krvnim mononuklearnim ćelijama, T ćelijama i limfocitnim tumorskim ćelijskim linijama. Nedavno je pronađeno da izlaganje oralnim keratinocitima i epitelnim ćelijama HIV-1 uzrokuje povećani SLPI protein i mRNA, čak i u odsustvu infekcije. Tako povećanje SLPI-a virusom može imati zaštitnu ulogu protiv HIV infekcije usne šupljine[9,10].

SLPI je takođe uključen u inhibiciju prenosa HIV-1 kroz majčino mleko. Veći SLPI pljuvačke kod odojčadi bio je povezan sa smanjenom transmisijom HIV-a kroz majčino mleko[11]. Slično tome, veći SLPI u vaginalnoj tečnosti bio je povezan sa smanjenom perinatalnom transmisijom HIV-a[9].

Mehanizam inhibicije: Čini se da inhibicija HIV-a od strane SLPI uključuje inhibiciju internalizacije HIV-a vezivanjem za Aneksin 2, molekul ćelijske površine. Pošto se vezivanje HIV-a za Aneksin 2 može prekinuti od strane SLPI, predtretman sa SLPI teoretski može inhibirati infekciju. Do sada nije pokazan efekat SLPI protiv drugih retrovirusa[12].

SLPI u karcinomima

SLPI je prekomerno izražen u mnogim vrstama karcinoma, uključujući rak jajnika, pluća i dojke. On je uključen u progresiju tumora[13]. Devogoodt i sar.[14] su otkrili da je SLPI regulisan ginekološkim karcinomima i da može poslužiti kao marker. Kod tumora, proteaze imaju važnu ulogu u lokalnom razaranju tkiva i širenju tumora. To podrazumeva da antiproteaze poput SLPI treba da ograniče širenje tumora. Međutim, pronađeno je da je SLPI konstantno povišen kod tumora pluća, jetre i jajnika i da je povezan sa povećanom malignom aktivnošću. Pokazalo se da SLPI izaziva proliferaciju ćelija in vitro[15]. Međutim, ova promaligna aktivnost je rezultat uloge antiproteaze, a ne proliferacionih stimulativnih svojstava[15]. Sayers i sar.[16] su pokazali da se SLPI reguliše u visoko metastatskim ćelijama karcinoma dojke. SLPI sprečava degradaciju progranulina, enzima povezanog sa proliferacijom ćelija i povećane invazivnosti u ćelijama raka dojke[16].

SLPI is the most effective anti-HIV-1 factor among the innate inhibitory molecules in saliva[4]. It is believed to inhibit HIV-1 transmission through oral secretions.

In 1995, McNeely demonstrated that HIV-1 infection in monocytes was blocked by human saliva[2,8]. SLPI was the only molecule in saliva which had antiretroviral activety at physiological concentrations[9]. This anti-HIV-1 activity of SLPI has also been seen in peripheral blood mononuclear cells, T cells and a lymphocyte tumour cell line. Recently, it was found that exposure of oral keratinocytes and epithelial cells to HIV-1 caused increased SLPI protein and mRNA even in the absence of infection. Thus increase in SLPI by the virus may have a protective role against HIV infection of the oral cavity[9,10].

SLPI is also implicated in inhibiting transmission of HIV-1 through breast milk. Higher salivary SLPI in infants was correlated with reduced HIV transmission through breast milk[11]. Similarly, higher SLPI in vaginal fluid was associated with decreased perinatal HIV transmission[9].

Mechanism of Inhibition: The inhibition of HIV by SLPI appears to involve inhibition of HIV internalisation by binding to Annexin II, a cell surface molecule. Since binding of HIV to Annexin 2 can be disrupted by SLPI, pretreatment with SLPI could theoretically inhibit infection. So far, no SLPI effect has been demonstrated against other retroviruses[12].

SLPI in cancers

SLPI is overexpressed in many cancers including ovary, lung and breast cancer. It has been implicated in tumour progression[13]. Devogoodt et al.[14] found that SLPI was upregulated in gynaecological cancers and could serve as a marker. In tumours, proteases have an important role in local tissue destruction and tumour spread. This implies that anti proteases like SLPI should restrict the spread of tumour. However, it has been found that SLPI is consistently elevated in tumours of the lung, liver and ovary and associated with increased malignant activity. SLPI has also been shown to cause cell proliferation in vitro[15]. However, this pro malignant activity is due to its role as an anti protease rather than its proliferation stimu-lating properties[15]. Sayers et al.[16] demonstrated that SLPI is upregulated in highly metastatic breast carcinoma cells.

Stepien i sar.[17] istraživali su serumski SLPI kod pacijenata kojima je dijagnostikovan papilarni karcinom tiroidne žlezde i multinodularna guša. Otkrili su da je SLPI značajno povećan kod ispitanika sa karcinomom, dok su slučajevi multinodularne gušavosti imali SLPI uporediv sa kontrolama. Povećana ekspresija SLPI navedenih karcinoma bila je povezana sa lošom prognozom[18].

Karcinomi povezani sa virusom humanog papiloma

Humani Papilloma virus (HPV) je uzročnik karcinoma grlića materice . Odnedavno se njegova uloga široko proučava u oralnim i orofaringealnim karcinomima[19]. Studije su otkrile da se karcinom krajnika i orofarinksa češće povezuje sa HPV -om nego sa oralnim karcinomom. Pušači i osobe koje žvaću duvan imali su manje šanse da imaju HPV pozitivne tumore nego nepušači i žvakači[19,20].

Pošto SLPI ima anti-HIV aktivnost, njena uloga je takođe istraživana u HPV pozitivnim tumorima. Istraživanja su pokazala da je SLPI značajno smanjen u metastazama u poređenju sa ne -metastatskim karcinomima skvamoznih ćelija glave i vrata (HNSCC). Dakle, viši SLPI korelira sa zaštitom od HPV infekcije. Takođe, povećana ekspresija receptora za Aneksin 2 zabeležena je kod visokorizičnih HPV pozitivnih HNSCC, što znači da bi povećan SLPI mogao da obezbedi zaštitu od HPV-a vezivanjem sa Aneksinom 2[21]. Ove studije pokazuju povezanost između SLPI i HPV u HNSCC. Pokazalo se da je SLPI inverzno povezan sa HPV pozitivnim tumorima. Inverzna povezanost HPV i SLPI sugeriše da povećani SLPI ima zaštitni efekat protiv HPV infekcije. In vitro studije su pokazale da blokiranje receptora aneksina A 2 sa SLPI uzrokuje smanjen ulazak HPV u ćelije[21].

Ustanovljeno je da pušenje povećava delovanje SLPI, što je verovatno razlog zašto je manje verovatno da će pušači razviti HPV pozitivne HNSCC[21]. Pierce Campbell i sar.[22] otkrili su da veći salivarni SLPI može pove -ćati rizik od HNSCC kod pušača

Hoffman i sar.[23] istraživali su vezu između ekspresije SLPI, HPV infekcije i bolesti limfnih čvorova kod karcinoma glave i vrata. Oni su takođe istraživali delovanje SLPI i navike vezane za duvan u normalnoj mukozi pacijenata bez HNSCC. Otkrili su da HPV pozitivni slučajevi imaju nisku ekspresiju SLPI.

SLPI prevents degradation of progranulin, an enzyme associated with cell proliferation and increased invasiveness in breast cancer cells [16] Stepien et al.[17] investigated the serum SLPI in patients diagnosed with papillary thyroid cancer and multinodular goitre. They found that SLPI was significantly increased in the subjects with cancer while multinodular goitre cases had SLPI comparable to controls. Increased SLPI expression the above cancers were associated with a poor prognosis[18].

Human Papilloma Virus Associated Cancers

Human Papilloma Virus (HPV) is the causative agent of cervical cancer. Recently, its role is being widely studied in oral and oropharyngeal carcinomas[19]. Studies have revealed that cancer of the tonsil and oropharynx is more commonly associated with HPV than oral cancers. Smokers and tobacco chewers were less likely to have HPV positive tumours than non-smokers and chewers[19,20].

Since SLPI has anti HIV activity, its role has also been investigated in HPV positive tumours. Studies have shown that SLPI was significantly decreased in metastatic as compared to non-metastatic head and neck squamous cell carcinomas (HNSCC). Thus, higher SLPI correlated with protection against HPV infection. Also, increased expression of Annexin 2 receptor was noted in high risk HPV positive HNSCC implying that increased SLPI could confer protection against HPV by binding with Annexin 2[21]. These studies demonstrate an association between SLPI and HPV in HNSCC. Further, SLPI has been shown to be inversely correlated with HPV positive tumours. An inverse association of HPV and SLPI suggests that increased SLPI has a protective effect against HPV-infection. In vitro studies have demonstrated that blocking of Annexin A2 receptor with SLPI causes reduced HPV entry into cells[21].

Smoking was found to increase SLPI expression which is the probable reason why smokers are less likely to develop HPV positive HNSCC[21] Pierce Campbell et al.[22] found that higher salivary SLPI might increase risk of HNSCC among smokers.

Hoffman et al.[23] investigated the relation between SLPI expression, HPV infection, lymph node disease in head and neck cancer.

Takođe su otkrili da je u jednom slučaju, kada je HPV bio pozitivan i da je SLPI bio visok, bila prisutna bolest čvorova. Pretpostavili su da se zaštitni efekat SLPI može izgubiti u HPV infekciji . Veća ekspresija SLPI kod pušača dovodi do smanjenja HPV infekcije i mogućeg kasnijeg pojavljivanja HNSCC u ve zi sa navikama.

Herpes Simplex virus (HSV)

Identifikovane su dve vrste HSV; HSV 1 koji uzrokuje orofaringealne infekcije i HSV 2 koji utiče na anogenitalne lokacije[1]. Do kraja 1970-ih smatralo se da je etiološki agens u cervikalnom i oralnom karcinomu Herpes Simplex virus. Iako je visokorizični HPV sada identifikovan kao uzrok karcinoma grlića mate - rice, HSV se smatra važnim kofaktorom u njegovoj pojavi[24]. Svetska prevalencaija OSCC-a, koja je bila pozitivna za HSV-1, bila je oko 15%; najveća prevalenca ija od 55% zabeležena je u Velikoj Britaniji. Industrijske zemlje imaju veći HSV-1 pozitivan OSCC u poređenju sa zemljama u razvoju[1].

Istraživanja su pokazala trostruko povećanje rizika od razvoja karcinoma grlića ma - terice kod pacijenata koji su seropozitivni za visokorizične HPV (hrHPV) i HSV-2 nasuprot hrHPV. Ispitanici pozitivni na HPV infekciju koji su takođe seropozitivni na HSV -1 imaju dvostruko veći rizik od razvoja karcinoma skvamoznih ćelija u poređenju sa HSV1-seronegativnim osobama sa sličnom izloženošću HPV-u. Ovi nalazi pokazuju da HSV i HPV mogu delovati sinergistički u razvoju karcinoma[24].

Infekcija HSV-2 povećava rizik od dobijanja HIV-a[9]. In vitro studije su pokazale da SLPI sprečava HSV infekciju vezivanjem za epitelne ćelije. Tačan mehanizam ove akcije još nije poznat[9]. Fakioglu i sar.[9] su dokazali da i HSV-1 i HSV-2 smanjuju SLPI i tako izbegavaju lokalni imuni sistem. HSV može uzrokovati ovo smanjenje bilo sprečavanjem oslobađanja SLPI, smanjenjem ekspresije gena ili izazivanjem njegove degradacije[9]. Uobičajeno prihvaćena metoda je regulacija SLPI mRNA i virusna degradacija[9].

HSV-1 i HSV-2 mogu uzrokovati smanjenje SLPI, čak i u prisustvu aciklovira koji zavisi od rane ekspresije HSV i nezavisno od replikacije virusa[24]. HSV-1 može smanjiti ekspresiju SLPI brže od HSV-2; tako HSV-1 infekcija anogenitalnog regiona može da promoviše hrHPV. Regulacija SLPI može takođe povećati stvaranje NF -Kb, što će dalje pro - movisati HSV infekciju. Smanjenje SLPI u prisustvu HSV infekcije može takođe promovisati sticanje HIV-a[9].

They also investigated SLPI expression and tobacco related habits in normal mucosa of patients without HNSCC. They found that HPV positive cases had low SLPI expression. They also found that in one case where HPV was positive and SLPI was high, nodal disease was present. They postulated that the protective effect of SLPI may be lost in HPV infection. Higher expression of SLPI in smokers leads to decreased HPV infection and probable later onset of habit associated HNSCC.

Herpes Simplex Virus (HSV)

Two types of HSV are identified; HSV 1 which causes oropharygeal infections and HSV 2 which affects anogenital sites[1]. Until the late 1970s, it was believed that the aetiological agent in cervical and oral cancers was herpes simplex virus. Though high risk HPV is now identified as the cause in cervical cancer, HSV is considered as an important cofactor in its occurrence[24].The worldwide prevalence of OSCC which were positive for HSV-1 was around 15%; the highest prevalence of 55% was seen in the United Kingdom. Industrialised nations have greater HSV-1 positive OSCC when compared to developing countries[1].

Studies have revealed threefold increase in the risk of developing cervical cancer in patients who are seropositive for high risk HPV (hrHPV) and HSV-2 versus hrHPV alone. Further, subjects testing positive for HPV infection who are also seropositive for HSV-1 have a twofold increased risk of developing oral squamous cell cancer on comparison with HSV-1-seronegative individuals with similar HPV exposure. These findings show that HSV and HPV may act synergistically in cancer development[24].

Infection with HSV-2 increases the risk of acquiring HIV[9]. In vitro studies have shown that SLPI prevents HSV infection by binding to epithelial cells. The exact mechanism of this action is not known yet [9]. Fakioglu et al[9] proved that both HSV-1 and HSV-2 decrease SLPI thereby evading the local immune system. HSV could cause this decrease either by preventing release of SLPI, decreasing gene expression or by causing its degradation[9]. The commonly accepted method is by downregulation of SLPI mRNA and by viral degradation[9].

HSV-1 and HSV-2 can cause decrease in SLPI even in the presence of acyclovir which is dependent on early gene expression of HSV

Epstein Barr Virus

Epstein Barr Virus (EBV) je bio prvi humani virus koji je identifikovan sa većim onkogenim potencijalom. EBV pogađa skoro 90% odraslih širom sveta. Povezan je sa oralnom vlasastom leukoplakijom, Burkittovim limfomom, nazofaringealnim karcinomom, karcinomom skvamoznih ćelija i infektivnom mononukleozom[25]. Pošto EBV klasično utiče na epitelne ćelije u usnoj duplji , nazofarinksu i pljuvačnim žlezdama, postoji sumnja da je uključen u premaligne lezije i kod oralnih skvamoznih karcinoma[1].

Međutim, EBV detekcija u OSCC-u je varijabilna, možda zbog etničkih i geografskih varijacija[1]. Ekspresija SLPI je ispitivana među EBV pozitivnim pacijentima koji imaju karcinom nazofarinksa (NPC). SLPI mRNA je značajno smanjena u NPC u poređenju sa normalnim epitelom, dok je ekspresija SLPI mRNA i proteina veća u EBV negativnim ćelijama. To podrazumeva zaštitnu ulogu SLPI u NPC-u povezanom sa EBV[18].

Kod NPC, lokalna upala je veoma važan uzročni faktor. SLPI ima jake antiinflamatorne sposobnosti, posebno inhibiranjem oslobađanja NF-Kb, oslobađanja histamina iz mastocita i C5a iz upaljenih pluća. Tako smanjenje SLPI može promovisati NPC[18].

and independent of replication of the virus[24]. HSV-1can decrease SLPI expression faster than HSV-2; thus HSV-1infection of the anogenital region can promote hrHPV. Downregulation of SLPI can also increase NF-Kb formation which will further promote HSV infection. The reduction of SLPI in the presence of HSV infection may also promote acquirement of HIV[9].

Epstein Barr Virus

Epstein Barr Virus (EBV) was the first human virus identified as having oncogenic potential. EBV affects almost 90% adults worldwide. It is associated with oral hairy leukoplakia, Burkitt's lymphoma, nasop-haryngeal cancer, oral squamous cell carcinoma and infectious mononucleosis[25]. Since EBV classically affects epithelial cells in the oral cavity, nasopharynx and salivary glands, there has been a suspicion that it is involved in premalignant lesions and in oral squamous cell carcinomas (OSCC)[1]. However, EBV detection in OSCC has been variable possibly due to ethnic and geo-graphical variations[1]. SLPI expression has been studied among EBV positive patients having nasopharyngeal carcinoma (NPC). SLPI mRNA was significantly downregulated in NPC when compared with normal epithelium while mRNA and protein expression of SLPI were higher in EBV negative cells. This implies a protective role of SLPI in EBV associated NPC[18].

In NPC, local inflammation is a very important causative factor. SLPI has strong anti-inflammatory abilities especially by inhibiting of release of NF-Kb, histamine release from mast cells and C5a from inflamed lung. Thus SLPI decrease can promote NPC[18].

Zaključak

HPV, HSV i EBV su virusi koji su uključeni u HNSCC. SLPI je antiproteaza sa antiinflamatornim, antibiotskim i antivirusnim svojstvima. Povećana SLPI ima zaštitnu ulogu u virusnoj onkogenezi, dok smanjeni nivoi povećavaju verovatnoću virusne infekcije. HSV infekcija smanjuje ekspresiju SLPI i može promovisati virusne infekcije. Prema tome, SLPI ima potencijal i kao biomarker u karcinomima, ali i kao potencijalni cilj za buduće terapije kako bi se sprečio karcinom izazvan virusom.

Sukob interesa: Ne
Finansijska podrška: Ne

Conclusion

HPV, HSV and EBV are viruses implicated in HNSCC. SLPI is an antiprotease with anti-inflammatory, antibiotic and antiviral properties. Increased SLPI has a protective role in viral oncogenesis while decreased levels increase the probability of viral infection. HSV infection decreases SLPI expression and can promote viral infections. Thus, SLPI has potential both as a biomarker in cancers as well as a potential target for future therapies to prevent virus induced cancers.

Conflict of Interest: Nil
Financial Support: Nil.

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