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REVIEW

- 59 Potential role of micro ribonucleic acids in screening for anal cancer in human papilloma virus and human immunodeficiency virus related malignancies

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ABOUT COVER

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Potential role of micro ribonucleic acids in screening for anal cancer in human papilloma virus and human immunodeficiency virus related malignancies

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Abstract

Despite advances in antiretroviral treatment (ART), human immunodeficiency virus (HIV) continues to be a major global public health issue owing to the increased mortality rates related to the prevalent oncogenic viruses among people living with HIV (PLWH). Human papillomavirus (HPV) is the most common sexually transmitted viral disease in both men and women worldwide. High-risk or oncogenic HPV types are associated with the development of HPV-related malignancies, including cervical, penile, and anal cancer, in addition to oral cancers. The incidence of anal squamous cell cancers is increasing among PLWH, necessitating the need for reliable screening methods in this population at risk. In fact, the currently used screening methods, including the Pap smear, are invasive and are neither sensitive nor specific. Investigators are interested in circulatory and tissue micro ribonucleic acids (miRNAs), as these small non-coding RNAs are ideal biomarkers for early detection and prognosis of cancer. Multiple miRNAs are deregulated during HIV and HPV infection and their deregulation contributes to the pathogenesis of disease. Here, we will review the molecular basis of HIV and HPV co-infections and focus on the pathogenesis and epidemiology of anal cancer in PLWH. The limitations of screening for anal cancer and the need for a reliable screening program that involves specific miRNAs with diagnostic and therapeutic values is also discussed.

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Core Tip: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. People living with human immunodeficiency virus (HIV) are at high risk of acquiring HPV infection and developing HPV-associated malignancies, including anal cancer, independent of acquired immune deficiency syndrome. This high risk is associated with several factors including the dysregulation of cellular micro ribonucleic acids (miRNAs) and the direct interaction between HIV and HPV. Dysregulated miRNAs are known to play a role in HIV, HPV infections, and HPV-related cancers. Here, we discuss the role of HIV in HPV-associated pathogenesis and important implications of miRNAs on current screening for and early detection of anal cancer.

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INTRODUCTION

At the end of 2019, approximately 36900000 people were estimated to be living with human immunodeficiency virus (HIV)[1]. Despite the advances in antiretroviral treatment (ART) and the increase in number of patients accessing ART since 2010, cancer mortality in people living with HIV (PLWH) remains high[2]. Mortality from HIV associated illnesses decreased substantially since its peak in 2004 mainly due to a decrease in the incidence of opportunistic infections. With the introduction of highly active ART in 1996, there has been a substantial improvement of clinical outcomes in PLWH[3-5]. This has brought an increase in life expectancy and a change in the age distribution of PLWH[6,7]. The risk of developing cancer increases with age; and as PLWH are now aging, the burden of cancer has substantially increased in this population. Since the beginning of the epidemic, HIV was associated with Kaposi's sarcoma, aggressive B-cell lymphomas, and invasive cervical cancer. Diagnosis of these cancers in PLWH confers the diagnosis of acquired immune deficiency syndrome (AIDS) and are thus termed as AIDS-defining cancers. Other types of cancers are non-AIDS defining, such as anal carcinoma, Hodgkin lymphoma, hepatocellular carcinoma, and lung cancer. These have been increasingly recognized to occur in PLWH and have become a leading cause of death[8-11]. One reason behind the increase in the rate of non-AIDS defining cancers in PLWH is increased prevalence of oncogenic viruses in this population, one of which is human papilloma virus (HPV) [12].

HPV is the most common sexually transmitted viral disease in both men and women worldwide[13]. HPV targets epithelial cells and includes more than 200 types that exist with genomic differences. About 40 types specifically infect the anogenital epithelium and upper digestive tract, among which 15-20 types are considered as high-risk HPV (HR-HPV), including HPV16 and HPV18[14]. Oncogenic or HR-HPV types are associated with the development of high-grade intraepithelial lesions and consequently, cancers of the anogenital region and oropharynx. About 99.9% of cervical cancers and 80%-90% of anal squamous cell cancers (ASCC) are associated with infection with HR-HPV[15]. While the incidence of cervical cancer has remained stable over the years, the incidence of ASCC has increased, particularly in PLWH[16]. With these increasing trends, it is imperative to screen for anal cancer in this high-risk population. However, many of the currently used screening methods, including the Pap smear, are invasive and require specialized equipment. In addition, the Pap smear is neither specific (specificity is approximately 75%) nor sensitive (approximately 55%)

[17]. Thus, identification of non-invasive and more effective methods is crucial.

Micro ribonucleic acids (miRNAs) have emerged as clinically useful molecular biomarkers for better management and treatment of many types of cancers. In HPV-associated cancers, miRNAs have been shown to be deregulated and involved in the pathogenesis of the disease. Given that the molecular mechanisms involved in anal cancer development during HIV infection are still unclear, characterization of miRNA expression in the context of HIV infection and anal cancer and the identification of relevant biomarkers could help elucidate the potential role of HIV and HPV in the progression of ASCC, as well as help prevent and treat anal cancer.

In this review, we will focus on the mechanisms and pathogenesis underlying HIV and HPV infections and the epidemiology and risk factors of anal cancer. We will also discuss the need for anal cancer screening, especially in HIV-infected individuals and the potential implementation of miRNAs as screening and therapeutic tools in high-risk populations.

HIV INFECTION

HIV-1 is the causative agent of AIDS. HIV-1 is a retrovirus whose genome is composed of 2 copies of single-stranded RNA molecules. HIV genome has 9 open reading frames and encodes for precursor proteins that give rise to 15 viral proteins. These proteins can be classified into structural and regulatory. The structural proteins include Gag, Env, and Pol. The matrix, capsid (CA), nucleocapsid, and p6 proteins are generated from Gag precursor and make up the core of the virus particle. The Env polyprotein is subsequently processed to generate the envelope proteins, gp120 and gp41. The *pol* gene encodes viral enzymes: Protease (PR), reverse transcriptase, and integrase. The HIV genome also encodes essential regulatory elements, Tat and Rev, and accessory regulatory proteins: Vif, Vpr and Nef[18].

HIV envelope glycoprotein mediates HIV cell entry by binding to its primary receptor, CD4 molecule, expressed on target cells, such as CD4+ T cells, monocytes, and macrophages. HIV entry also requires binding a chemokine coreceptor, CCR5 or CXCR4[19]. Viral entry is followed by reverse transcription of the viral RNA genome, integration of the provirus into cellular genome, synthesis of viral genome, and assembly and budding of the newly formed virions. When no new viral proteins are produced, infected cells can revert to latency[20].

HIV targets and kills CD4+ T cells, monocytes, macrophages, and microglial cells, however the main targets of HIV infection and subsequent destruction are the CD4+ T cells[21,22].

The mechanisms underlying CD4+ T cell death are still not well defined. The permissivity status of CD4+ T cells during HIV infection determines the pathway by which these cells die (Figure 1). Abortively-infected[23,24], productively infected[25-28], and HIV-uninfected (bystander) CD4+ T cells undergo cell death through different mechanisms[27].

HIV INFECTION AND CD8+ T CELL RESPONSES

In addition to progressive CD4 lymphopenia, HIV infection is also associated with impaired HIV-specific CD8+ T cell responses. CD8+ T cells play an important role in eliminating viruses. Recognition of infected cells occurs through T cell receptor that binds processed viral antigen expressed by major histocompatibility complex (MHC) I molecules on the surface of infected cells. Recognition is followed by a cascade of activation events leading to the release of granzymes and perforin and killing of infected cell. Activated CD8+ T cells also release anti-viral cytokines that act to control viral replication[29]. Despite the over activation of the immune system during HIV infection, it seems that HIV-specific CD8+ T cell responses fail to clear viral infection [30-32] and this can be attributed to several factors. HIV-infected cells sometimes revert to latency and are known to act as viral reservoirs. In this case, the absence of HIV protein expression on the surface of infected cells hinders recognition by CD8+ T cells[33]. Interestingly, several studies have shown that HIV proteins are capable of escaping CD8+ T cell recognition by modulating the expression of MHC I on surface of infected cells (Figure 2)[34]. Andrieu *et al*[35] showed that the Nef protein can down-regulate surface MHC I expression on DC, thereby impairing CD8+ T-cell maturation. In addition, HIV viruses are prone to rapid mutations which enables them to escape immune surveillance[36,37]. Chronic immune stimulation can have adverse effects on

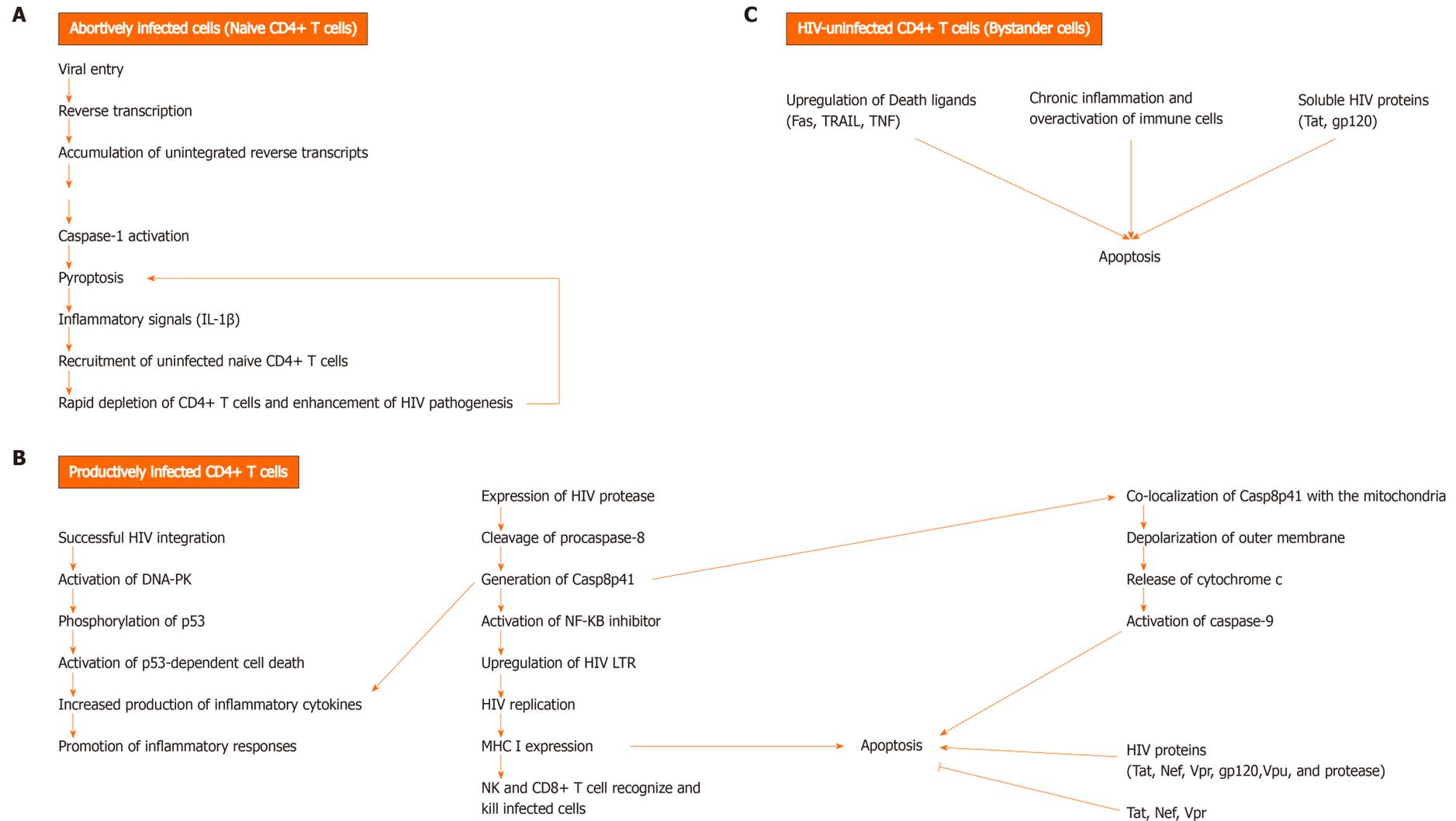


Figure 1 Mechanisms of CD4+ T cell death during human immunodeficiency virus infection. A: Unsuccessful human immunodeficiency virus (HIV) infection can lead to HIV-infected CD4+ T cell death by pyroptosis, an inflammatory programmed cell death that occurs via caspase-1 activation. As a result, inflammatory signals, such as Interleukin-1β are released. The accumulation of unintegrated reverse transcripts, following viral entry and reverse transcription, can indirectly activate caspase-1 and induce pyroptosis in resting CD4+ T cells with abortive viral infection. Pyroptosis is thought to greatly contribute to the rapid depletion of CD4+ T cells and development of chronic inflammation, as a result of proinflammatory cytokine release from dying CD4+ T cells, which in turn causes the recruitment of uninfected and naïve CD4+ T cells into the lymphoid tissues. These cytokines trigger pyroptosis in the recruited cells, leading to a vicious cycle of inflammation, thereby enhancing HIV pathogenesis by creating an overactive immune environment and further cell death; B: Cell death can occur in productively infected CD4+ T cells, following successful HIV integration and expression of HIV protease (PR). HIV PR can cleave cellular

procaspase-8 and generate Casp8p41. This fragment activates the transcription factor NF-kappaB inhibitor and thus, induces HIV replication by upregulating HIV long terminal repeats (LTRs). Casp8p41 expression promotes inflammatory responses by enhancing the production of pro-inflammatory cytokines. Besides, Casp8p41 induces apoptosis by directly co-localizing with the mitochondria and depolarizing its outer membrane. The subsequent release of cytochrome c from mitochondria leads to activation of caspase 9 and cell death. Another mechanism by which viral integration triggers cell death is through the activation of deoxyribonucleic acid-dependent protein kinase, resulting in phosphorylation of p53 and activation of p53-dependent cell death program. HIV Tat, Nef, and Vpr can have both pro- and anti- apoptotic effects. On the other hand, gp120, Vpu, and protease have pro-apoptotic effects. HIV-infected cells can be killed by cytotoxic lymphocytes, natural killer cells and CD8+ T cells, which become highly active during infection; C: HIV-uninfected cells, known as bystander cells, usually die by apoptosis during the course of infection, due to either: upregulation of death ligands (Fas, TRAIL, TNF), activation-induced cell death due to chronic inflammation and over activation of immune cells, or direct cytotoxic effects of soluble HIV proteins (Tat, gp120). DNA-PK: DNA-dependent protein kinase.

CD8+ T cell function. Several inhibitory molecules (Figure 2) are expressed by CD8+ T cells during chronic inflammation, and therefore impair the function of HIV-specific CD8+ T cell response[38]. Importantly, a small fraction of CD8+ T cells become infected with HIV and are susceptible to the direct cytotoxic effects of the virus[39,40]. It has also been shown that CD8+ T cell counts begin to decline during late stages of infection[41]. The pro-apoptotic properties of HIV gp120 protein may contribute to this decline[42,43]. Several studies showed that CD4+ T cell loss also impacts the function of CD8+ T cell, whereby CD4+ T cells are required to maintain cell-mediated immune responses against HIV[44,45]. Tregs, a subpopulation of CD4+ T cells that have a regulatory and suppressive role in autoimmune diseases and cancer, have been shown to contribute to the progression of AIDS disease by inhibiting HIV-specific CD4+ and CD8+ T cell responses[46].

HPV GENOME

HPV can deregulate cellular proteins, including p53 and Retinoblastoma protein (pRb), thus mediating epithelial transformation and malignancy. HPV genome consists of a circular DNA that encodes the early proteins E1, E2, E4, E5, E6, and E7, and the late proteins L1 and L2 (Figure 3). E1 and E2 play an important role during HPV replication by binding to the viral replication origin, whereas E4 proteins are involved in virion release. E5, E6, and E7 are viral oncoproteins whose increased expression and activity is associated with enhanced proliferation of HPV-infected epithelial cells. L1 and L2 are structural proteins that form the viral capsid[47].

HPV INFECTION AND CD8+ T CELL RESPONSES

CD8+ T cells play a key role in the immune responses against HPV. *In vivo* studies using mouse models have shown that cells expressing HPV-16 E6 and E7 antigens are recognized and killed by cytotoxic T lymphocyte (CTL) cells[48,49]. In fact, E7-specific CTLs were detected in lesions containing tumor cells[50]. CD8+ T cells recognize viral antigens presented by MHC I/peptide complexes expressed on the surface of infected cells. However, this interaction is not sufficient to induce the killing of the infected cell.

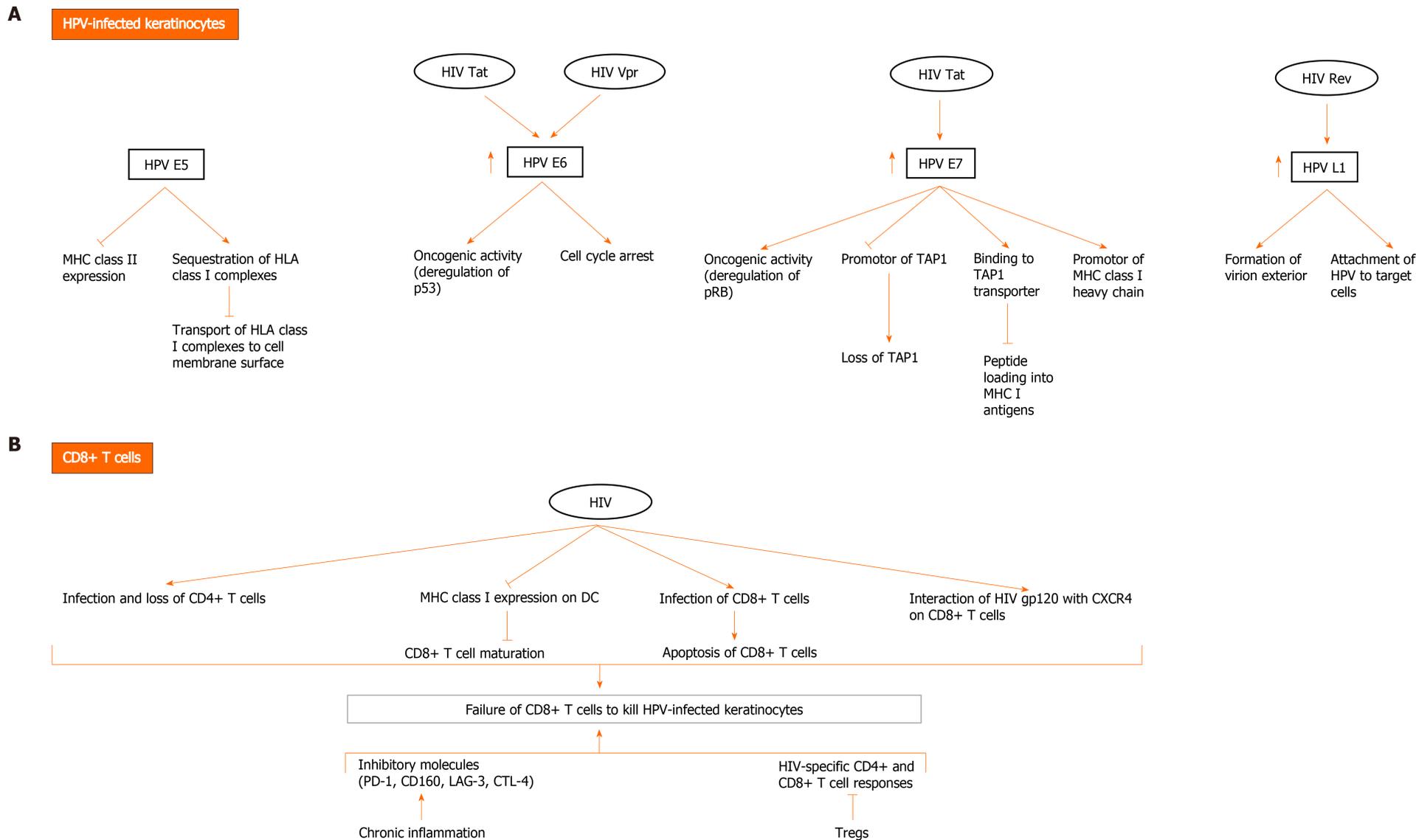


Figure 2 Possible mechanisms of direct and indirect interactions between human papillomavirus and human immunodeficiency virus to evade the immune system and mediate human papillomavirus carcinogenesis. A: Human immunodeficiency virus (HIV) and human papillomavirus (HPV) contribute to HPV-related carcinogenesis and evasion of immune cells through several mechanisms involving direct interaction between HIV and HPV proteins

in HPV-infected keratinocytes. HPV E5 oncoprotein downregulates major histocompatibility complex (MHC) II expression and sequesters human leukocyte antigen (HLA) class I complexes in keratinocytes, thereby blocking transport of HLA class I complexes to cell membrane surface. HPV E6 exerts oncogenic effects, mainly through deregulation of p53 and induction of cell cycle arrest. HPV E7 exerts oncogenic activity through deregulating pRB. It promotes downregulation of MHC class I expression through downregulating peptide transporter 1 associated with antigen processing (TAP1) and binding to TAP transporter, and thus inhibiting peptide loading into MHC I antigens. It also downregulates promoter of MHC I heavy chain. Importantly, HIV Tat upregulates the expression of HPV16 E6 and E7, enhancing their oncogenic effects. It also increases the expression of HPV L1. HIV Rev indirectly upregulates HPV L1 expression. HIV Vpr interacts with HPV E6 protein to induce cell cycle arrest and oncogenesis; B: HIV infection diminishes immune response to HPV infection, resulting in HPV persistence and pathogenesis. Failure of CD8+ T cells to kill HPV-infected keratinocytes is a major event in HIV and HPV co-infection and occurs through multiple mechanisms. In addition to loss of CD4+ T cells due to infection with HIV, downregulation of MHC I expression on dendritic cells (DC) by HIV inhibits CD8+ T cell maturation. A small fraction of CD8+ T cells become infected with HIV and are susceptible to the direct cytotoxic effects of the virus. Moreover, HIV gp120 interacts with CXCR4 on CD8+ T cells and affects their function. Other factors also contribute to inhibition of HIV-specific CD4+ and CD8+ T cell responses and include activation of Tregs and the expression of inhibitory molecules (programmed death-1 [PD-1], CD160, lymphocyte activation gene 3, cytotoxic T lymphocyte antigen-4 [CTLA-4]) by CD8+ T cells during chronic inflammation induced by HIV.

Signaling from activated dendritic cells and virus specific CD4+ T cells is highly important for stimulating and maintaining an efficient CTL activation[51]. It has been reported that peripheral blood mononuclear cell (PBMC) cultures from healthy individuals showed HPV16-specific CD4+ T-cell and CTL responses directed against HPV16 E2, E6 and/or E7[52-55]. Activated circulatory CD4+ and CD8+ T cells migrate from peripheral blood to infected tissues in healthy individuals[56]. Interestingly, these responses are mostly detected in women without cervical intraepithelial neoplasia (CIN)[57], and less commonly in women with CIN[54]. Nakagawa *et al*[55] also showed that the absence of CTL response to E6 proteins is associated with persistence of HPV16 infection in HPV-infected women without squamous intraepithelial lesions. HPV deregulates MHC I expression during infection (Figure 2). Multiple studies have reported the down regulation of MHC I expression in cervical cancer cells[57] and laryngeal papilloma[58]. This may be due to the loss of the peptide transporter 1 associated with antigen processing (TAP1), whose promoter appears to be downregulated by HPV 16 and 18 E7. The latter proteins also downregulate the promoter of MHC class I heavy chain[59]. A study has documented that HPV 11 E7 binds to the TAP transporter protein, thereby blocking peptide loading into MHC I antigens[60]. Other studies have reported that HPV 16 E5 plays a role in sequestering human leukocyte antigen class I complexes in the Golgi apparatus, which thus prevents their transport to the cell membrane surface[61]. The expression of MHC II is also modulated during HPV infection and carcinogenesis. MHC II are usually expressed by antigen presenting cells only however, it has been shown that keratinocytes, in cervical premalignant lesions and cancer, upregulate the expression of MHC II, because of the production of pro-inflammatory cytokines. On the other hand, HPV 16 E5 can block the expression of these molecules[62].

Nevertheless, the induction of a systemic T cell-mediated response against HPV proteins (E6, E7, and others) results in successful viral clearance in healthy individuals. In contrast, HIV infection leads to a progressive loss of CD4+ T cells[63]. Thus, even though antigen presenting cells express and present HPV peptides on their cell surface, in the absence of CD4+ T cell, CD8+ T cells fail to maintain their activity and thus, fail to kill HPV-infected cells.

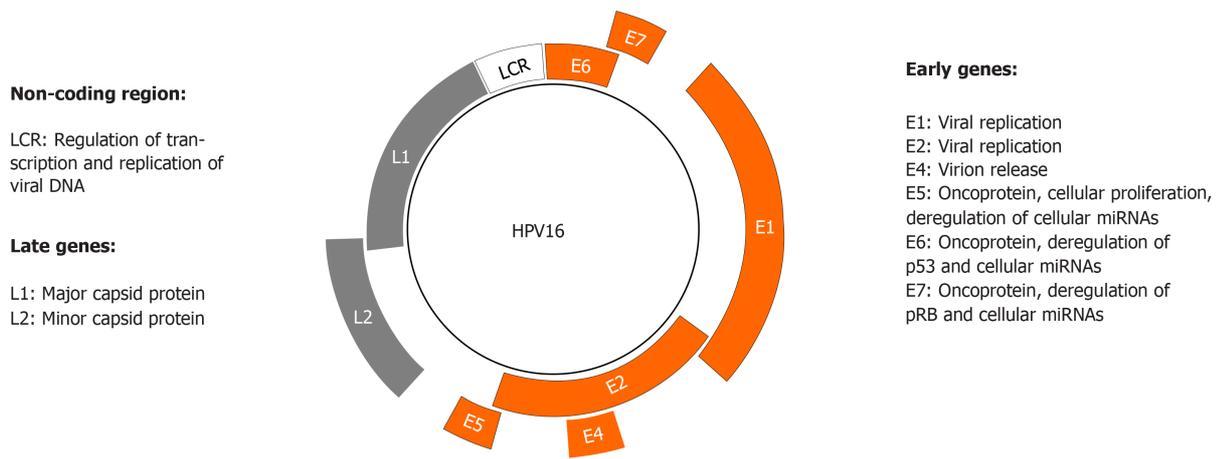


Figure 3 Human papillomavirus genome organization and function. Human papillomavirus (HPV) has a circular double-stranded genome, which is divided into three regions: early, late, and non-coding long control region. The latter regulates transcription and replication of viral deoxyribonucleic acid. The early and late regions encode eight proteins whose major functions are shown.

HPV and HIV have developed a wide spectrum of mechanisms to evade immune responses. Given the ability of both viruses to modulate cellular pathways in infected and uninfected cells, and thus immune surveillance and responses [64], many mechanisms of immune evasion may be possible (Figure 2). HIV infection may directly or indirectly result in protecting HPV-infected keratinocytes from CTL-mediated killing. Therefore, HIV may affect both keratinocytes and CD8+ T cells, and thus favor HPV pathogenesis. Importantly, HIV proteins have been shown to interact with HPV proteins directly and indirectly by enhancing their expression and/or activation, promoting cancer [65-68]. HIV Tat increases the expression of HPV16 E6 and E7, enhancing their oncogenic effects. It also increases the expression of HPV L1, which forms the exterior of the virion and mediates initial attachment to target cells [65,66]. Rev indirectly upregulates HPV L1 expression [67]. Vpr interacts with HPV E6 protein to induce cell cycle arrest in cervical cancer cells [68]. However, evidence of interaction between the two viruses remains scarce and needs further investigation.

ANAL SQUAMOUS CELL CANCER PATHOGENESIS

ASCC are cancers that arise in the transitional or squamous zone of the anal canal and are mostly caused by HPV16 and 18. It is believed that the basal layer cells in the epithelium of this transitional zone can become infected with HPV after the occurrence of micro-abrasions. Most individuals who acquire HPV mount the appropriate immune response and clear HPV infection within a year. However, HPV may persist in others and could lead to either low-grade or high-grade (HSIL) squamous intraepithelial lesions, and can be further classified into anal intraepithelial neoplasia (AIN) 1, 2 or 3 [69,70].

ANAL SQUAMOUS CELL CANCER EPIDEMIOLOGY AND RISK FACTORS

Anal cancer is uncommon with 48541 new cases reported worldwide in 2018 as by the GLOBOCAN estimates [71]. However, its epidemiology has changed over the past 2 decades. A steady increase in the incidence and prevalence rates of ASCC has been reported. In the United Kingdom, a 70% increase in its incidence rates has been noted since the early 1990s [72]. The United States has reported similar trends with a 2.9% increase in incident rates each year since 1975 [73]. In 2021, there will be an estimated 9090 new anal cancer cases and 1430 new anal cancer deaths [74]. The increase in incidence has been associated with multiple factors that include lifetime number of sexual partners, smoking, receptive anal intercourse, genital warts, and infection with HIV [75-77]. More than 90% of ASCCs have been found to be related to HPV, mainly HPV 16 and 18. Among men, the highest proportion of HPV is in men who have sex with men (MSM) and ranges between 50%-60% [76,78]. This proportion is even higher in HIV-infected MSM and reaches 90% in some studies [79,80]. Additionally, this

population is infected with multiple HR-HPV types[81,82]. Not surprisingly, the prevalence of HSIL and anal cancer mirrors that of anal HPV in these populations where the incidence of neoplasia is higher than that of the general population. Compared to heterosexual men, MSMs have a 20 times increased risk of developing ASCC. HIV-positive MSMs have an even greater risk[76].

An obvious relationship between HIV, HPV, and anal cancer was illustrated in a population study in the United States between 1980-2005[73]. Authors found that HIV infection had a strong impact on the trends of anal cancer among males where incidence rate increased by 3.4% annually overall and by 1.7% in those without HIV-infection. A meta-analysis of 53 studies by Machalek *et al*[76] assessed the prevalence and incidence of HPV, AIN, and anal cancer in MSM and reported a substantial difference between HIV-positive and HIV-negative men for prevalence of any type of HPV ($P = 0.005$), including any HR-HPV ($P = 0.01$), prevalence of any anal cytological abnormality ($P = 0.005$), and low-grade anal lesions ($P = 0.01$). Analysis of recent studies reporting on histological abnormalities, high-grade AIN, and anal cancer revealed a significant difference between HIV-positive MSM *vs* HIV-negative MSM [76]. In another study, the incident rate for anal cancer was reported to be 69 per 100,000 person-years (PY) in HIV-positive MSMs *vs* 14 per 100,000 PY in HIV-negative MSMs[83]. Contrary to AIDS defining cancers, whose rates have decreased after the introduction of ART, the incidence rates of ASCC have shown an increase by 3%[8,76, 84]. This may be attributable to a longer lifespan of PLWH allowing them to live longer with oncogenic HPV giving time for the development of HSIL and ASCC. In addition, PLWH have been found to have multiple types of HPV with Müller *et al*[82] reporting PLWH having a 7 times higher risk of having multiple types of HPV as compared to HIV-negative individuals.

The link between a lower rate of HR-HPV clearance and development of ASCC in PLWH is still being investigated. Studies have shown that in HIV-positive individuals, HR-HPV infection is cleared at a slower rate than HIV-negative individuals. Geskus *et al*[85] observed that HPV16 had the lowest clearance for both prevalent positive and incident positive infection. Additionally, authors reported a decreasing clearance rate with increasing HIV viral load. Results from a recently updated meta-analysis showed that clearance rate of HPV infection among PLWH was approximately half compared to that of HIV-negative individuals, with similar findings reported for HR-HPV[86]. Whether CD4 count affects the clearance rate or not is not well established. In the same meta-analysis above, Looker *et al*[86] reported a possible, but non-significant, reduction in clearance of HPV with lower CD4 counts. In a nested case-control study from the Swiss HIV Cohort Study, lower CD4 counts in PLWH were correlated with the development of ASCC. Authors reported that the best predictor was a CD4 count 6-7 years prior to ASCC diagnosis. Beyond that point, authors found that the ASCC risk was less sensitive to CD4 counts, highlighting the importance of starting ART early before the establishment of precancerous lesions[87].

ANAL CANCER AND SCREENING

There are no formal guidelines on anal cancer screening due to the lack of trials assessing the effectiveness of such screening practices. However, with the accumulating evidence of an increasing incidence of anal cancer in PLWH, there is increased advocacy for screening in these high-risk populations, drawing on the proven value of cervical cytology in reducing cervical cancer. Additionally, cost-effective models of screening MSM for AIN every 2-3 years have shown possible gains in life-expectancy and quality of life[88,89].

Screening consists of detection and treatment of anal HSIL. Detection can be done through anal cytology, digital rectal examination, high resolution anoscopy (HRA), and/or biopsy. While some experts have advocated the use of HRA for initial screening because of the high prevalence of AIN in PLWH and MSM, anal cytology remains a preferred initial method due to limited availability of HRA especially in developing countries[64]. Yet, all the previously mentioned tools have several limitations and disadvantages. For example, HRA is invasive, and cytology is neither sensitive nor specific. Therefore, a non-invasive method with high sensitivity and specificity for detection of precancerous and cancerous anal lesions is needed.

ROLE OF MIRNAS AS POTENTIAL BIOMARKERS FOR ANAL CANCER SCREENING IN PLWH

Circulatory and tissue miRNAs have become of interest to investigators, as these small non-coding RNAs possess distinctive properties that make them ideal biomarkers for detection and prognosis of cancer. They play an important role in gene regulation by inducing the degradation and inhibiting the translation of the corresponding mRNAs [90,91]. They can also activate the expression of genes by targeting their promoters [92,93]. They are well known for their pleiotropic effects in many important cellular processes, such as apoptosis, proliferation, and differentiation [94]. They are significantly stable in the circulation, as well as in plasma and serum [95]. miRNAs are dysregulated in many cancers, including HPV-related cancers and their deregulation contributes to pathogenesis of disease [96-98]. Although several miRNAs were identified in different types of cancer, they have not been used in clinical practice, possibly due to the lack of standardized methods, often leading to contradicting data [98,99]. Exosome-encapsulated miRNAs are currently investigated to overcome the challenges associated with free-circulating miRNAs [100,101].

Globular profiling of miRNAs in cancer and normal tissues has been established in different types of cancers, including breast [102], lung [103], colon, liver, and pancreatic [104] cancers, which have allowed for the identification of a series of miRNAs that are deregulated in these cancers. However, an invasive method, such as surgery and biopsy collection, is needed to analyze the tissues. Thus, researchers are investigating the use of plasma and serum miRNAs as potential circulatory biomarkers for different purposes. This would allow for non-invasive quantification of these biomarkers and potentially for detection of premalignant lesions and screening of early tumorigenesis. In the context of HPV-associated cancer, miRNAs have been studied and documented as mediators or suppressors of pathogenesis [96,97,105]. Some of these miRNAs have been shown to be deregulated by HPV E5, E6, and E7 oncoproteins in different cells and tissues (Table 1). By downregulating p53, E6 alters the expression of many miRNAs that are transcribed by p53. On the other hand, E7 releases E2F transcription factor from pRB-E2F complex by degrading pRB. As a result, E2F becomes free to activate the transcription of many miRNAs. The mechanism by which E5 deregulates cellular miRNAs is still unclear [106]. The deregulation of many of these miRNAs was shown to affect several hallmarks of cancer, including enhanced proliferation, inhibition of apoptosis, invasion, and metastasis. A recent study showed that miR-129 was significantly upregulated in the serum and cervical cancer tissues collected from 72 patients, suggesting the possibility of using this miRNA as a biomarker for the detection of cervical cancer. Interestingly, HPV typing detected HPV16 in all cancer samples studied [107]. Another study identified a miRNA signature panel consisting of 9 miRNAs (miR-9, miR-15b, miR-20a, miR-31, miR-93, miR-183, miR-184, miR-222, and let-7b) with a combined area under the curve of 0.89 for CIN3 detection in HPV-positive self-samples of women with CIN3 [108]. Recently, Shi *et al.* [109] identified an optimal subset of 7 signature miRNAs, including miR144, miR147b, miR2182, miR425, miR451, miR483, and miR486 in cervical cancer. Functional enrichment analysis showed that the latter miRNAs are involved in carcinogenic pathways, such as Wnt signaling pathway and transforming growth factor- β signaling pathway. Importantly, altered miRNAs have been investigated mainly in cervical cancer cell lines [96] and cervical carcinoma samples [110]. However, miRNAs have been less studied in anal cancer and a single study showed that HPV16-E7 protein is capable of inducing miR-15b in anal carcinoma biopsies [111].

HIV infection also dysregulates cellular miRNA biogenesis and expression profiles [112-114]. For example, HIV Tat and Vpr affect miRNA biogenesis by binding Dicer or Drosha [115-117], while trans-activation response modulates TRBP, an important component of the miRNA generation complex. HIV infection is known to both upregulate and downregulate several cellular miRNAs in HIV-infected human PBMC, T cells, monocyte-derived macrophages (MDMs), latently infected CD4+ T cells, plasma samples, HUT78 cells, and CD4+ T cells from either acute or chronic HIV-infected individuals. Few studies determined the expression of cellular miRNAs in HIV-infected cell lines (Table 2). Recently, Biswas *et al.* [118] established a comparative global miRNA expression profile in human PBMC and MDMs infected with HIV-1/HIV-2. Differentially expressed miRNAs were identified in these cells. Pathway analysis using Kyoto Encyclopedia of Genes and Genomes database showed that the deregulated miRNAs are likely to be involved in p53 signaling pathway, PI3K-Akt signaling pathways, Mitogen-activated protein kinase signaling pathways, FoxO signaling pathway, and NF-kappaB inhibitor signaling pathway, all of which play a

Table 1 Cellular micro ribonucleic acids deregulated by human papillomavirus proteins

HPV protein	miRNA target	miRNA expression level	Sample type	Biological effect(s)	Ref.
E5	miR-146a	+	E5-expressing HaCat cells	Promoted cell proliferation	[106]
	miR-203	-	E5-expressing HaCat cells	Increased expression of p63	[106]
	miR-324-5p	-	E5-expressing HaCat cells	Contributed to cervical carcinogenesis	[106]
E6	miR-20a	+	CaSki and SiHa (HPV16+) human cervical cell lines	Promoted cell growth through downregulating PDCC6 and activating Akt and p38	[156]
	miR-20b	+	HeLa (HPV18+), SiHa and Caski human cervical cancer cell lines; Cervical carcinoma tissues	Reduced TIMP2 expression and induced EMT, migration, and invasion	[157]
	miR-23b	-	SiHa and CaSki cell lines	Increased expression of uPA and induction of migration in human cervical cancer cells	[158]
	miR-30c-2*	-	HPV-infected NSCLC; TL1 cell line	Correlated with tumor stage and lymph node metastasis	[159]
	miR-34a	-	CaSki and SiHa cell lines, HPV18-positive cell lines HeLa and C411, HPV68-positive cell line ME180Cervical cancer tissues	Inhibited cell proliferation; Increased LDHA expression levels, inhibited Warburg effect and reprogrammed glycolysis through targeting LDHA	[160,161]
	miR-145	-	Hela, SiHa, and CaSki cell lines; Cervical cancer tissues	Modulated invasion and therapy resistance of cervical cancer cells	[162]
	miR-195	-	HeLa and SiHa cell line cervical cancer tissue samples	Promoted cell proliferation, invasion, and metastasis	[163]
	miR-218	-	HPV16 positive cervical cell lines and tissues; Cervical cancer tissues	Increased expression of LAMB3, SFMBT1, and DCUN1D1, promoted EMT, migration, and invasion in cervical cancer associated with clinicopathological characteristics of patients	[164,165]
	miR-375	-	SiHa and CaSki cell lines; Cervical tissue samples	Modulated EMT in cervical cancer; Enhanced invasion and metastasis of cervical carcinoma cells through targeting SP1	[166,167]
	miR-2861	-	SiHa and CaSki cell lines; Cervical cancer tissues	Enhanced cell proliferation and invasion, and inhibited apoptosis in cervical cancer cells; Negatively associated with advanced tumor stage and lymph node metastasis	[168]
	E7	miR-15b	+	HPV16 E7-expressing tumors from anal carcinoma patients; CaSki cell line	Downregulated cyclin E1; Increased expression of several E2F-regulated genes
miR-20a		+	OSCC tissues	Inhibited cell proliferation, invasion, and migration	[169]
miR-21		+	HPV16 E7-transfected HeLa cells; Cervical cancer tissue	Enhanced cervical carcinoma cell proliferation, growth, and invasion; Involved in cervicitis and cervical cancer progression	[170,171]
miR-25		+	HVK-derived raft tissues infected with either HPV16 or HPV18	Increased expression correlated with the progression of the cervical lesions, making it a potential biomarker for CINs and cervical cancer	[96]
miR-27b		+	HPV 16-positive human cervical carcinoma tissues; SiHa and CaSki cell lines	Reduced PLK2 expression; Promoted cell proliferation and inhibited paclitaxel-induced cell apoptosis; Inhibited PPAR γ expression and promoted proliferation and invasion	[172,173]
miR-205		+	HPV-positive keratinocytes	Activated Akt pathway and upregulated cyclin D1 levels, resulting in increased proliferation	[174]
miR-323		+	Cervical cancer cell lines transfected with HPV 16 E7 and SiHa cervical cancer cells	---	[175]
E6/E7	miR-16	+	HFK-derived raft cultures with HPV16	---	[96]

		infection; HVK-derived raft tissues infected with either HPV16 or HPV18; CIN3 and Cervical carcinoma tissues with HR HPV infection		
miR-22	-	HVK-derived raft tissues infected with either HPV16 or HPV18	Suppressed tumor growth and metastasis	[96,176]
miR-24	+	HPV-positive keratinocytes	Reduced p27 expression level and enhanced proliferation	[174]
miR-29a	-	HVK-derived raft tissues infected with either HPV16 or HPV18	---	[96]
miR-92a	+	CIN and cervical carcinoma tissues with HR HPV infection, and raft tissues with HPV16 or HPV18 infection	Increased expression correlated with the progression of the cervical lesions, and may serve as a biomarker for CINs and cervical cancer	[96]
miR-100	-	HFK-derived raft cultures with HPV18 infection	---	[96]
miR-125a	-	Cervical carcinoma tissues SiHa and HeLa cell lines	Increased STAT3 expression and enhanced tumorigenesis and metastasis	[177]
miR-146a-5p	-	HPV16 E6/E7-positive keratinocytes; HeLa, SiHa, and CaSki cell lines	Enhanced expression of KDM2B; Promoted proliferation and migration	[178]
miR-203	-	NHKs and NFKs expressing E6, E7, or combination	Increased expression of p63 and promotion of cell proliferation	[179,180]
miR-378	+	CIN3 and cervical carcinoma tissues with HR HPV infection, and raft tissues with HPV16 or HPV18 infection	---	[96]

“+”: Upregulated; “-”: Downregulated; miRNAs: Micro ribonucleic acid; HPV: Human papillomavirus; PDCD6: Programmed cell death 6; TIMP-2: Tissue inhibitor of metalloproteinase 2; EMT: Epithelial to mesenchymal transition; NSCLC: Non-small cell lung cancer; LDHA: Lactate dehydrogenase A; LAMB3: Laminin 5 β 3; SFMFBT1: Scm-like with four MBT domains 1; DCUN1D1: Defective in cullin neddylation 1; Domain containing 1; OSCC: Oral squamous cell carcinoma; HVK: Human vaginal keratinocytes; PLK2: Polo-like kinase2; CIN: Cervical intraepithelial neoplasia; HFK: Human foreskin keratinocytes; CIN3: Cervical intraepithelial neoplasia 3; HR HPV: High risk HPV.

role in carcinogenesis[118,119]. HIV Tat, Nef, and Vpr have been reported to alter the expression levels of many miRNAs and contribute to HIV pathogenesis (Table 3). On the other hand, cellular miRNAs also target HIV genome, but it is still unclear whether these miRNAs are effective during HIV infection[112].

Overall, molecular mechanisms that contribute to anal cancer pathogenesis and progression are still elusive. One of the reasons that little progress has been made in understanding the mechanisms of carcinogenesis in this type of cancer is the scarcity of *in vitro* and *in vivo* model systems for investigating anal cancer. Thus, further studies are required to gain insight into the mechanisms involved in anal cancer. This is particularly important as these mechanisms may involve miRNAs, which may be further investigated as potential targets for cancer therapy. The use of miRNA-based therapeutics has been investigated in clinical trials in several countries. MicroRNA mimics and anti-miRNAs (antagomirs) are now under investigation as potential therapeutic agents for multiple cancers. miRNA mimics may be administered to replace downregulated miRNAs, which usually act as tumor suppressors in cancers. On the other hand, many miRNAs have been targeted for inhibition in the treatment of several cancers. These miRNAs are referred to as oncomiRs and their overexpression in cancer contributes to pathogenesis. In the context of cervical cancer, Lee *et al*[110] showed that treatment with anti-miR-199a suppressed cervical cell growth *in vitro*. Additionally, a study has shown a promising role for the tumor suppressor miR-34a, which is downregulated in HPV-positive cancers, in repressing oncogenic transformations. Both miR-34a and miR-125 are downregulated in cervical cancer samples and correlate with cervical cancer invasiveness[120]. Interestingly, a recent phase 1 study of MRX34, a liposomal miR-34a mimic, was conducted with patients having advanced solid tumors[121]. Thereby, this miRNA may be a good candidate for treatment of HPV-related cancers, including anal cancer[122]. In addition, anti-miRs targeted at miR-122, which has been shown to be upregulated in HIV-1 infected Jurkat cells, reached clinical phase II trials and were investigated for treating hepatitis C infection [123]. Other candidate miRNAs are being tested in clinical trials, paving the way for developing miRNA-based drugs for treating several illnesses and cancer diseases[122, 124].

LIMITATIONS AND CONSIDERATIONS FOR THE USE OF MIRNAS AS BIOMARKERS FOR ANAL CANCER SCREENING

In the case of anal cancer, where HIV and HPV pathogenesis play a role in the development of the disease in PLWH, a major challenge is to distinguish HIV-specific miRNAs, HPV-specific miRNAs, and HIV and HPV co-infection-specific miRNAs. Major limitations include the absence of studies implementing computational models to identify these miRNAs, technical issues associated with conventional miRNA extraction and detection tools, and scarcity of anal cancer *in vitro* and *in vivo* models. Ongoing studies are still being conducted to study miRNA profiles during HIV[125-127] and HPV[128-130] infections. With the appropriate application of advanced bioinformatic analysis tools and computational models, the identification of the most predictive miRNAs, even from complex datasets would be possible. These tools are becoming widespread and have already been used to identify potential miRNA biomarkers for Ebola[131] and severe acute respiratory syndrome coronavirus 2[132], in addition, these tools have been used to decipher potential miRNA biomarkers in a wide variety of cancers, including melanoma[133,134], breast[135], colon[136], and lung cancer[137].

In addition to the conventional miRNA detection platforms which include Northern blotting, *in situ* hybridization, next generation sequencing, reverse transcription qPCR, and microarrays[138], new miRNA extraction and detection platforms have emerged to compensate for the limitations of conventional assays[139]. These technologies are referred to as point-of-care (PoC) technologies and include isothermal amplification-based assays[140], lateral flow assay-based systems[141], nanobead-based[142], electro-chemical-based[143], and microfluidic chip-based[144] strategies. The latter, which is also known as Lab-on-a-chip or microchip, is highly specific, cost-effective, and a quick approach for the multiplexed detection of miRNAs[139]. It has been used to test miRNAs in several biological samples, including blood of breast cancer patients [145]. Importantly, this system has been also used to quantify miRNAs in plasma extracellular vesicles (EVs), including exosomes. EVs are secreted by body cells and are found in body fluids including plasma, urine, and synovial fluid[146]. They have been shown to carry and stabilize miRNAs in the blood[147]. A unique feature of exosomes is the presence of cell-specific proteins[148], which enables identification of exosomes released from cancer cells. Examining specific miRNAs released from tumors and tumor niche, instead of whole blood miRNA profiling would provide a more accurate way of distinguishing HIV-specific and HPV-specific miRNAs, given the unique viral tropism of each. Exosomal miRNAs would enable the identification of the cell origin and might be a better source when compared to non-exosomal, cell-free miRNAs. Recently, studies that profiled and analyzed miRNAs from different sources were reviewed[149]. Authors concluded that 71% of the studies stated that exosomes are the best source of miRNAs as biomarkers. Detecting EVs miRNA signature has already been proven to be a good prognostic tool in several cancers including colorectal[150] and pancreatic cancer[151].

Interestingly, organ-on-chip and organoids are being used to study infectious diseases and cancer. These models can be used to assess HPV virus-Langerhans cells interactions[152] and HPV-oral mucosa epithelia interactions[153]. Cell-to-cell communication can be also studied by co-culturing cancer cells with immune cells, and thus allows the study of cancer-immune interaction. Organoids can be used to model tumor-derived EVs, also known as oncosomes, in addition to EVs released by stromal cells in tumor microenvironment[154]. Very recently, researchers established organoid cultures from human ecto-and endocervix. Cells collected using Pap brush method were used to derive organoids from cervical tissue. The established patient-derived model system resembled causative HPV infection[155], and thus could be used for modeling HPV-related pathogenesis, in addition to exploring the role of HPV and HIV in deregulating miRNAs. The same derivation method can be used to derive organoids from healthy or tumor anal tissue to assess miRNA deregulation by HIV and/or HPV. These model systems could be used to test the efficacy of engineered miRNA-loaded EVs in targeting anal cancer cells to deliver potential miRNA therapeutic molecules[156-180].

It is important to note that although extensive research has been conducted to identify candidate miRNA biomarkers for cancer screening, the development of new techniques, such as PoC for miRNA detection is still at the very early stage and a work on progress. Further progress is required to achieve the desired goal of using PoC testing for detecting and distinguishing miRNAs deregulated by oncogenic viral infections, including HPV. Therefore, the identification of miRNAs deregulated by

Table 2 Cellular micro ribonucleic acids deregulated during human immunodeficiency virus infection

Sample type	miRNAs deregulated	Ref.
PBMCs from HIV-infected patients	↑ miR-9; ↓ miR-29c, miR-31, miR-125b, miR-146b-5p, miR-150, Let-7g	[181]
T cells from HIV-infected individuals	↓ miR-16, miR-146b, miR-150, miR-223	[182]
HIV-1 infected PBMCs	↑ miR-223; ↓ miR-21, miR-26a, miR-29a, miR-29b, miR-29c, miR-155	[183]
HIV-1 infected PBMCs	↑ miR-3195, miR-3656, miR-4492, and miR-6087; ↓ miR-1273h-3p, miR-1273h-5p, miR-671-5p, and miR-7-5p	[118]
HIV-2-infected PBMCs	↑ miR-18a-3p and hsa-miR-320b	[118]
HIV-2-infected MDMs	↑ miR-542-3p, miR-375, miR-195-5p, miR-30c-2-3p, miR-4802-3p, and miR-26b-5p	[118]
HIV-1- and HIV-2-infected MDMs	↓ miR-148b-5p, hsa-miR-26a-2-3p, miR-199a-1, miR-199a-2, and miR-874-5p	[118]
HIV-1-transfected HeLa cells	↓ miR-16, miR-93, miR-148b, miR-221	[184]
HIV-1 infected Jurkat cells.	↑ miR-122, miR-297, miR-370, and miR-373; ↓ miR-17-5p and miR-20a	[185]
latently infected CD4+ T cells	↑ miR-196b and miR-1290	[186]
PBMCs obtained from HIV-1 positive individuals with high viral load	↑ miR19b, miR-34a, miR-144, miR-146a, miR-155, miR-382, miR-615-3p	[187]
Plasma obtained from patients with HIV infection	↓ miR-3162-3p	[188]
HIV-1-infected HUT78 cells and CD4+ T cells from chronic HIV-1 infected individuals	↓ Let-7 miRs	[189]
HIV-1 positive plasma samples in the acute stage infection	↑ miR-16-5p, miR-20b-5p, miR-24-3p, miR-142-5p, miR-195-5p, miR-206, miR-223-3p, miR-885-5p, and let-7 g-3p; ↓ miR-34c-3p, miR-181c-3p, miR-202-3p, and miR-409-3p	[190]
HIV-1 infected CD4+ T cells	↓ miR-20a and miR-106b	[191]

↑: Upregulation; ↓: Downregulation; miRNAs: Micro ribonucleic acid; HIV: Human Immunodeficiency virus; PBMC: Peripheral blood mononuclear cells; MDM: Monocyte-derived macrophages.

HIV, HPV, and HIV-HPV co-infection warrants further research. More accurate and standardized methods are required for implementation of miRNAs as biomarkers for anal cancer diagnosis[181-198]. Importantly, the widespread use of high-throughput sequencing, PoC technologies, and advanced computational analysis tools may facilitate discovering and distinguishing these miRNAs.

CONCLUSION

HPV is the most common sexually transmitted infection worldwide. PLWH are at high risk of acquiring HPV infection and developing HPV-associated malignancies, independent of AIDS. Anal cancer incidence, though rare in the general population, has been rising significantly in PLWH. The lack of standard screening programs contributes to the increased incidence of anal cancer, and thus, there is a need for anal dysplasia screening and treatment in PLWH. The discovery of highly sensitive and specific biomarkers would enable the early detection of anal cancer and the improved survival of HIV-infected patients. There is a need for relevant biomarkers that could be integrated into clinical practice and thus, aid in the detection, diagnosis, and treatment of high-risk patients. miRNAs have become valuable tools for detection and treatment of many types of cancer. Given their deregulation and potentially significant role in HPV-related pathogenesis and in HIV infections, miRNAs may serve as diagnostic and prognostic biomarkers that can enhance HIV patients' outcomes and provide better management of the disease. Genome-wide profiling of miRNAs and validation of miRNA targets in tissue and blood samples of people infected with HIV and HR-HPV is important to establish miRNA expression signatures in this population and would help develop non-invasive miRNA therapeutic strategies for treatment of anal cancer.

Table 3 Cellular micro ribonucleic acids deregulated by human Immunodeficiency virus proteins

HIV protein	miRNA target	Effect	Sample type	Biological effect	Ref.
Tat	miR-21, miR-29a, miR-222, miR-1290	+	Tat101-expressing Jurkat cells; Resting PBMCs from healthy donors were transiently transfected with Tat101-expressing vector	Targeted mRNAs of genes involved in apoptosis, T cell migration, and proliferation	[192]
	miR-128a, and miR-3182	-	Tat101-expressing Jurkat cells	---	[192]
	miR-132	+	Tat-transfected astrocytes and neurons, astrocytes from Tat-transgenic mice, and HIV-infected astrocytes	Involved in the direct neurotoxicity of Tat	[193]
	miR-129, miR-135a, miR-181a, miR-495, miR-523, miR-524, miR-539, let-7	-	U-87MG (astrocyte cell line), HEK 293T, and HeLa cells transfected with wild-type Tat	Downregulation of β -catenin activity	[194]
	miR-101	+	BMVECs exposed to Tat C	Decreased the expression of VE-cadherin	[195]
	miR-34a and miR-138	+	Astrocytoma cell line A172 and rat primary astrocytes exposed to Tat	Upregulated NF- κ B and promoted activation of astrocytes	[196]
Nef	miR-573 and miR-638	+	Human monocytic U937 cells that stably expressed HIV-1 Nef	Altered several pathways involved in HIV pathogenesis	[197]
	miR16-1, miR-18, miR-19a, miR-20a, miR-21, miR-27a, miR-29b, miR-125b, miR-146a, miR-146b-3p, miR-181a, miR-223, miR-570, miR-610 and miR-624	-	Human monocytic U937 cells that stably expressed HIV-1 Nef	Altered several pathways involved in HIV pathogenesis	[197]
	miR-17, miR-19a, miR-19b, miR-20a, miR26a, miR-28, miR-29a, miR-29b, miR-29c, miR-92a, miR-125b, miR-149, miR-150, miR-223, miR-324-5p, miR-378 and miR-382	+	Nef exosomes	Inhibited HIV replication	[197]
Vpr	miR-942-5p	+	PEL cells	Targeted I κ B α and activation of NF- κ B signalling	[198]
	miR-711	+	PEL cells	Directly targeted Notch1 and reduced levels of I κ B α transcript	[198]

“+”: Upregulation; “-”: Downregulation; miRNA: Micro ribonucleic acid; HIV: Human Immunodeficiency virus; HEK: Human embryonic kidney cells; BMVEC: Human brain microvascular endothelial cells; PEL: Primary effusion lymphoma; NF- κ B: NF-kappaB inhibitor.

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