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Malignancies in people living with HIV

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Abstract

Almost 40 years have passed since the first case of what is known as AIDS was documented. In these 40 years, AIDS has always been a research challenge and hot spot. Researchers and scientists have made tremendous progress in basic and clinical research on HIV. In particular, the widespread use of antiretroviral therapy (ART) has made it less of a deadly disease today and more of a manageable one. In the post- ART era when ART can significantly improve the immunity of people living with HIV (PLWH) and extend their life, the incidence of non-AIDS-defined cancers is greatly increased. Factors related to immunosuppression do not seem to explain this problem sufficiently. This suggests that besides immunosuppression, there are other mechanisms that may also contribute to the increased incidence of cancer in PLWH. Here, we summarized and discussed four possible mechanisms for the increased incidence of cancers in PLWH: immunosuppression, oncogenic viral infection, chronic infection, inflammatory damage, and the direct impact of HIV.

Keywords

Chronic inflammation. HIV. Immunodeficiency. Malignancy. Virus infection.

Introduction

In 1981, the first case of AIDS was reported in the world. 40 years have passed and great progress has been made in both basic and clinical research on AIDS. In particular, antiretroviral therapy (ART) is widely used. ART inhibits HIV replication and reduces the mortality of people living with HIV (PLWH). However, PLWH still have a higher risk of cancer development and a lower rate of cancer survival than non-HIV infected individuals[1]. Before the advent of ART, AIDS-defining cancers (ADCs) such as Kaposi's sarcoma (KS), cervical cancer, and non-Hodgkin's lymphoma (HL) occurred very frequently. With the wide use of ART, the incidence of ADCs decreased significantly, but the incidence of non-AIDS-defined cancers (NADCs) increased, such as lung cancer, hepatocellular carcinoma, and HL[2]. Nowadays, malignancies have become one of the leading causes of death in PLWH[3-5]. Therefore, there is an urgent need for strategies to prevent and control cancers in PLWH, and understanding the mechanisms by which HIV increases cancer incidence is certainly essential. Here, we summarize four possible mechanisms of increased tumorigenesis in PLWH: immunosuppression, oncogenic viral infection, chronic infection and inflammatory damage, and the direct role of HIV.

Immunodeficiency

Immunodeficiency is a recognized mechanism that explains a higher risk of cancer incidence in PLWH

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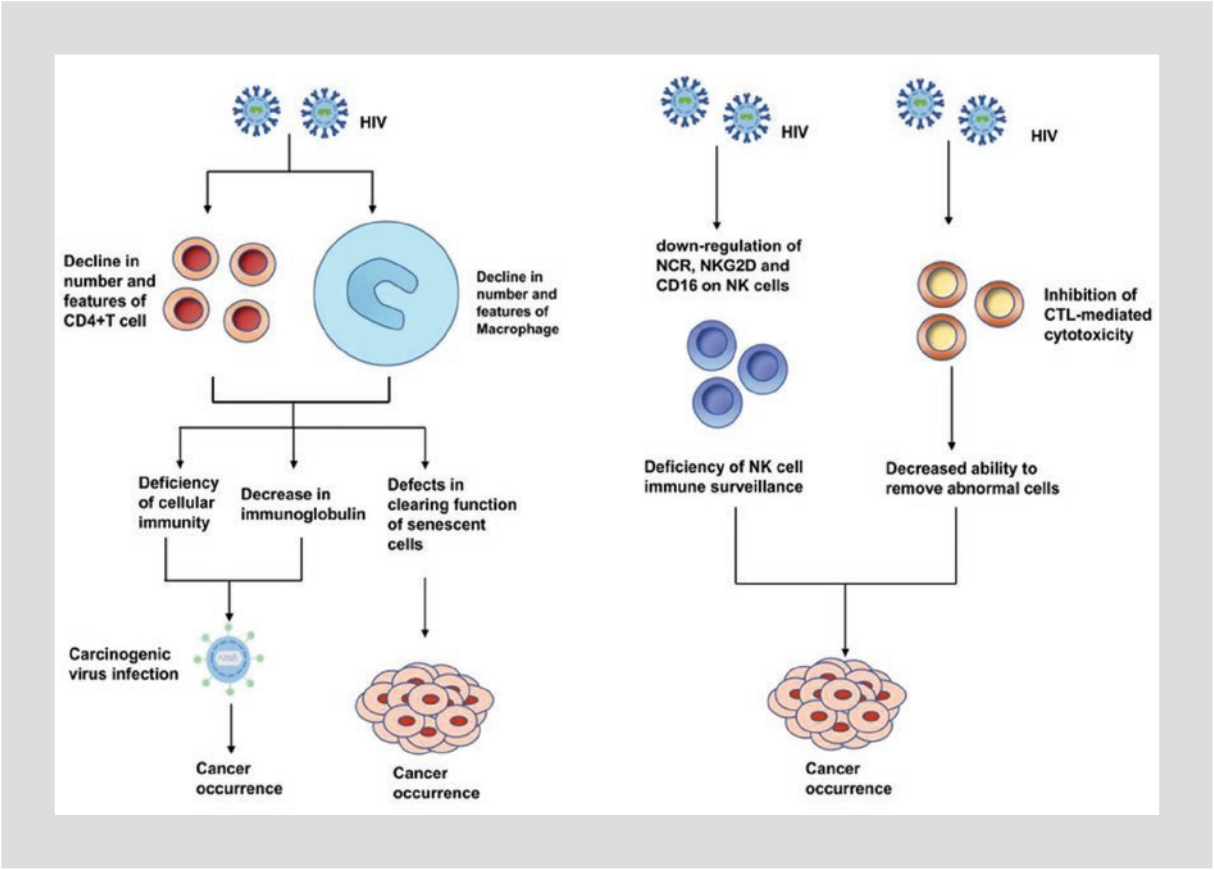

Figure 1. *Immune mechanism of a higher cancer risk in PLWH. Chronic HIV infection leads to a decrease in the number of CD4 + T cells and impaired function so that the body cannot produce effective cellular immunity, nor can it produce immunoglobulins to deal with potential infections. This will make the body more susceptible to certain infections of cancer-causing viruses. In addition, CD4 + T cells and macrophages are essential for eliminating senescent cells. In an abnormal immune system, senescent cells will promote tumor growth and metastasis. In addition, long-term exposure to HIV will lead to down-regulation of NCR, NKG2D and CD16 on NK cells, and thus NK cell recognition of abnormal cells through above receptors is defective. Another potential reason is that HIV can inhibit the cytotoxic response mediated by CTL. This inhibits the body's ability to eliminate abnormal cells. Chronic HIV infection can cause immunosuppression through the above-mentioned mechanisms and increase the risk of cancer.*

(Fig. 1). Immunodeficiency compromises immune surveillance. Numerous studies have demonstrated a negative correlation between CD4+T cell count and the risk of ADC and NADCs[1-3]. People with reduced CD4 cell counts are not able to produce an effective CD4+T cell response, nor are they able to produce immunoglobulin to deal with potential infections. Impaired T cell function leads to an increased susceptibility to human papillomavirus (HPV) infection and HPV associated malignancies[4]. Studies have shown that CD4+ T cells and macrophages are necessary to eliminate senescent cells, which is essential for cancer prevention and regression[5]. Without a functioning immune system, senescent cells will promote tumor growth and metastasis, although the underlying mechanism remains to be elucidated[6]. In addition, the decrease in natural killer (NK) cell-mediated immune surveillance in PLWH is mainly due to the long-term consequences of chronic HIV infection. Although the administration of inhibitory cART can partially restore the properties of NK cells, NK cells still undergo many functional and phenotypic changes related to HIV infection. As is well known, natural cytotoxicity receptors (NCR), natural-killergroup2, memberD (NKG2D), and CD16 receptors are involved in effective NK cell activation and cytotoxicity[7]. In chronic HIV infection and cancer, the recognition of abnormal cells by NK cells through above receptors is defective. This is mainly because long-term exposure to their respective ligands resulted in downregulation of NCR, NKG2D, and CD16 on NK cells[8]. Besides, women living with HIV are more likely to progress from a low-grade disease to a more severe one[9]. One potential reason is that HIV can inhibit cytotoxic T lymphocytes (CTL)-mediated cytotoxic responses; this inhibits the body's ability to clear

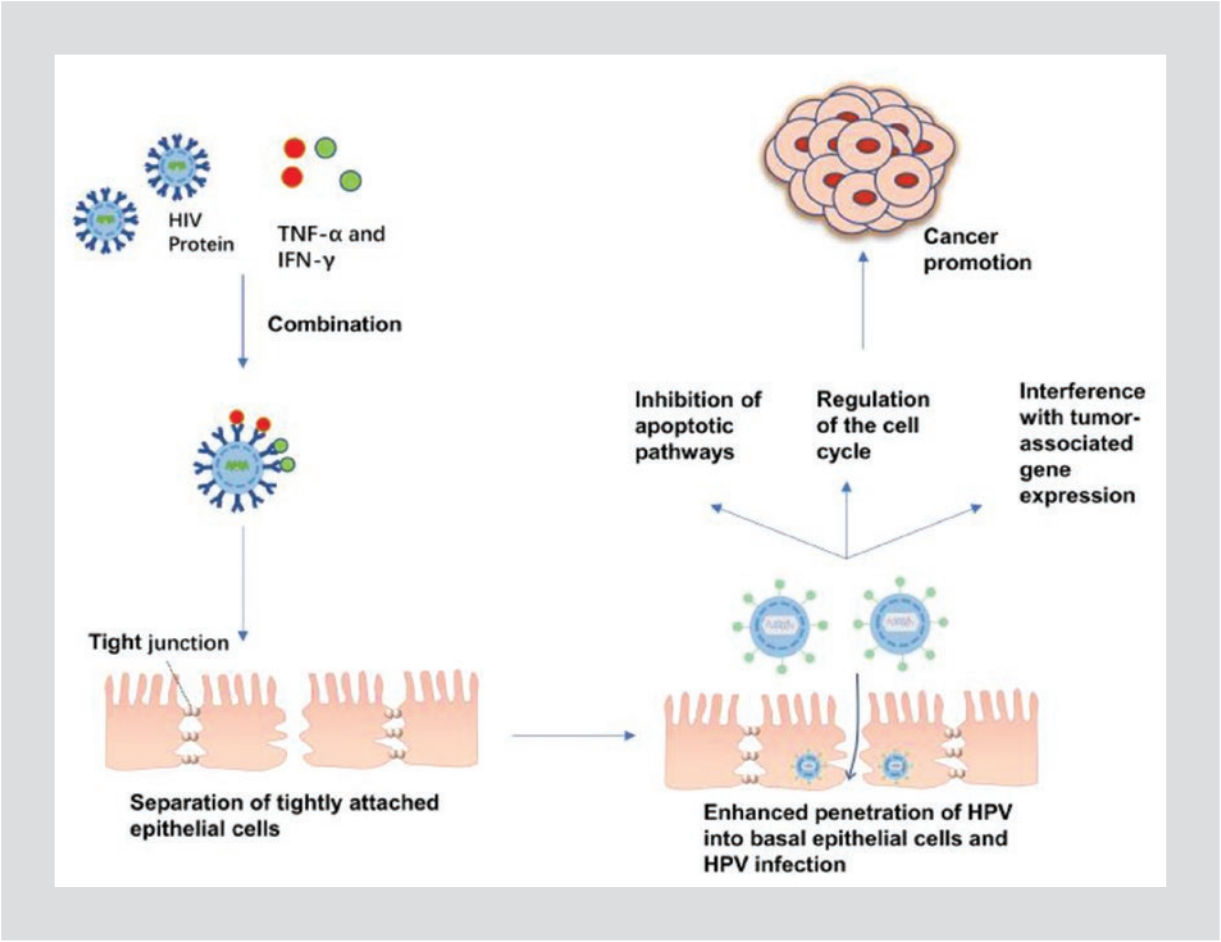

Figure 2. *The mechanism of tumorgenesis in HPV/HIV co-infected patients. HIV proteins (Tat and gp120) bind to cytokines (tumor necrosis factor-α, interferon-γ, and interferon-α) produced by HIV-infected cells. This leads to the separation of tight junctions along epithelial cells, which increases the penetration of HPV into the basal epithelial cells. HPV carcinogenesis involves multiple pathways, including apoptotic pathways and the pathways that regulate cell cycle or interfere with tumor-associated gene expression.*

abnormal cells, which, in turn, reduces the host's ability to block progression from HPV to advanced abnormal cytology (HSIL)[10]. Studies have shown that HIV co-infection reduces the clearance of HBV and HCV, increases the risk of chronic HCV infection and reactivation of latent HCV infection. This is all due to compromised NK cell activity in HIV infection[11-13]. Increased HBV/HCV viral load in HIV co-infection accelerates tumor progression through the expression of HBV/HCV viral proteins that are directly involved in cell transformation[14]. For example, HBV infection increases the chance of insertion mutations and thus the incidence of tumorgenesis. HIV-induced immune suppression is a potential mechanism by which HIV accelerates the progression of HPV infection to cervical cancer. A study of 151 women in Brazil found that HPV eradication took a significantly longer time in HIV-positive women (7.0 ± 3.8 months) than in negative women (5.9 ± 3.0 months) ($p < 0.05$). This suggests that HIV-mediated immune dysfunction can lead to a longer duration of HPV infection in the cervix and subsequent oncogenic transformation[15]. A prospective study by Konopicki et al. showed that $CD4^+$ count at more than 500 cells/ML for 18 months in HIV-positive women was associated with a reduced risk of high-risk HPV infection (odds ratio, 0.88; 95% CI: 82-0.94; $p = 0.0002$)[16].

However, HIV-infected patients with good immune reconstitution ($CD4^+$T cell count > 500/ml) still have a higher risk of HL and liver cancer than uninfected people[17]. Similarly, the incidence of anal cancer in PLWH is increased despite ART[18,19].

Viral infection

In the pathogenesis of AIDS-related malignancies, the complex interactions among different viruses or

concurrent multiple viral infections are important. Most ADCs and NADCs are related to viral infections[20]. Studies show that 40% of malignant tumors in PLWH are related to viral infections while this number is only 5% in the general population[21,22]. This may be because HIV has the same transmission route as some cancer-causing viruses, or because HIV suppresses host immunity making hosts susceptible to viral infections. It is worth noting that studies have shown that HIV proteins (Tat and gp120) together with the cytokines produced by HIV-infected cells (tumor necrosis factor-α, interferon-γ, and interferon-α) leads to compromised tight junctions along the epithelium and increased penetration of HPV to its target cells, the basal epithelial cells[23]. On the other hand, due to immunodeficiency women with HIV are particularly susceptible to HPV infection. The carcinogenesis of oncogenic viruses involves a variety of pathways, and they include the apoptotic pathway and the pathways that regulate cell cycle or interfere with the expression of tumor-related genes (Fig. 2)[24]. Recent studies have shown that certain miRNAs expressed by oncogenic viruses may promote the development of malignant tumors[25,26]. For example, EBV infection is associated with various types of lymphomas. The targets of EBV-encoded miR-BHRF1-1 include the tumor suppressor gene p53, and another miR-BART1 encoded by EBV is predicted to target Bcl-2, an anti-apoptotic gene. miRNAs synthesized by EBV either inhibit their translation or induce their degradation by binding to the mRNA targets. So EBV produces both miRNAs that may be pro-oncogenic (miR-BHRF1-1that inhibits p53 translation) and anti-oncogenic (miR-BART1 that inhibits Bcl-2 translation). EBV oncogenesis is the result of a trade-off between strict controls of cell proliferation signals[27]. EBV may also cause insertional mutations. Recent studies have shown that the integration of EBV occurs less randomly[28]. This non-random integration may be one of the factors leading to the onset of certain H-NHL because development of malignant tumors usually requires accumulating abnormal proliferation.

Chronic infection and inflammatory injury

Chronic inflammation greatly promotes cancer in PLWH. HIV infection induces a series of immune activation events[29]. Even with long-term virological suppression, inflammatory markers in HIV-infected individuals are still at a high level[19]. Studies have shown that the inflammatory response and cytokines induced by HIV infection may aggravate HBV/HCV-associated liver diseases[30,31]. HIV facilitates microbes in the intestine to migrate to the liver, which is reported to accelerate liver fibrosis[14] and therefore may play a role in the development of HBV/HCV associated hepatocellular carcinoma. Besides, some reports indicate that in patients with HBV/HIV co-infection, HIV-induced immunosuppression and persistent inflammation facilitates robust HBV/HCV replication and chronic viral hepatitis, which helps select out the viruses containing carcinogenicity enhanced mutations and subsequently increase the risk of liver cancer in these patients[32,33]. Besides, chronic antigen stimulation and inflammation will lead to polyclonal or oligoclonal proliferation of dysregulated B lymphocytes, which is also conducive to the abnormal secretion of cytokines such as IL-6 and IL-10 that promote the growth of B cells[34]. There are several mechanisms of chronic B cell activation in PLWH. First, chronic antigen stimulation of B cells in HIV infection itself may promote the excessive activation and transformation of B cells. Second, genetic mutations, chromosomal rearrangements (BCL-6 and c-MYC), and deletions (6q) in B cells have been shown to be related to chronic B cell activation due to chronic stimulation in viral infections (including EBV, HPV, and HCV) as well as mutations in Ras and p53 genes. Another proposed mechanism involves HIV-infected macrophages that provide B cells with stimulating signals leading to B cell activation and malignant transformation[35]. Finally, leakage of bacterial components and products from intestine into blood (microbial translocation) is considered a potential cause of chronic immune activation in PLWH[35]. These factors lead to continuous stimulation of B cells. Chronic polyclonal B cell activation is very important in the pathogenesis of AIDS associated non-Hodgkins lymphoma[36]. Besides, chronic B cell activation also contributes to B cell dysfunction and thus impairs de novo antibody responses, which may lead to the continuing growth of AIDS associated non- HL (Fig. 3)[37].

Recently, the significance of inflammatory biomarkers in predicting tumorigenesis in PLWH has been confirmed by a cohort study[38]. HIV proteins can induce the production of reactive oxygen species (ROS)[39]. The ROS themselves are weak carcinogens but are strong tumor promoters. Overproduction of ROS during an extended period of time leads to spontaneous tumor formation[39], indicating that ROS also participate in tumor formation in PLWH. A study showed that transient expression of HIV-1 reverse transcriptase (RT) in mammalian cells induced the

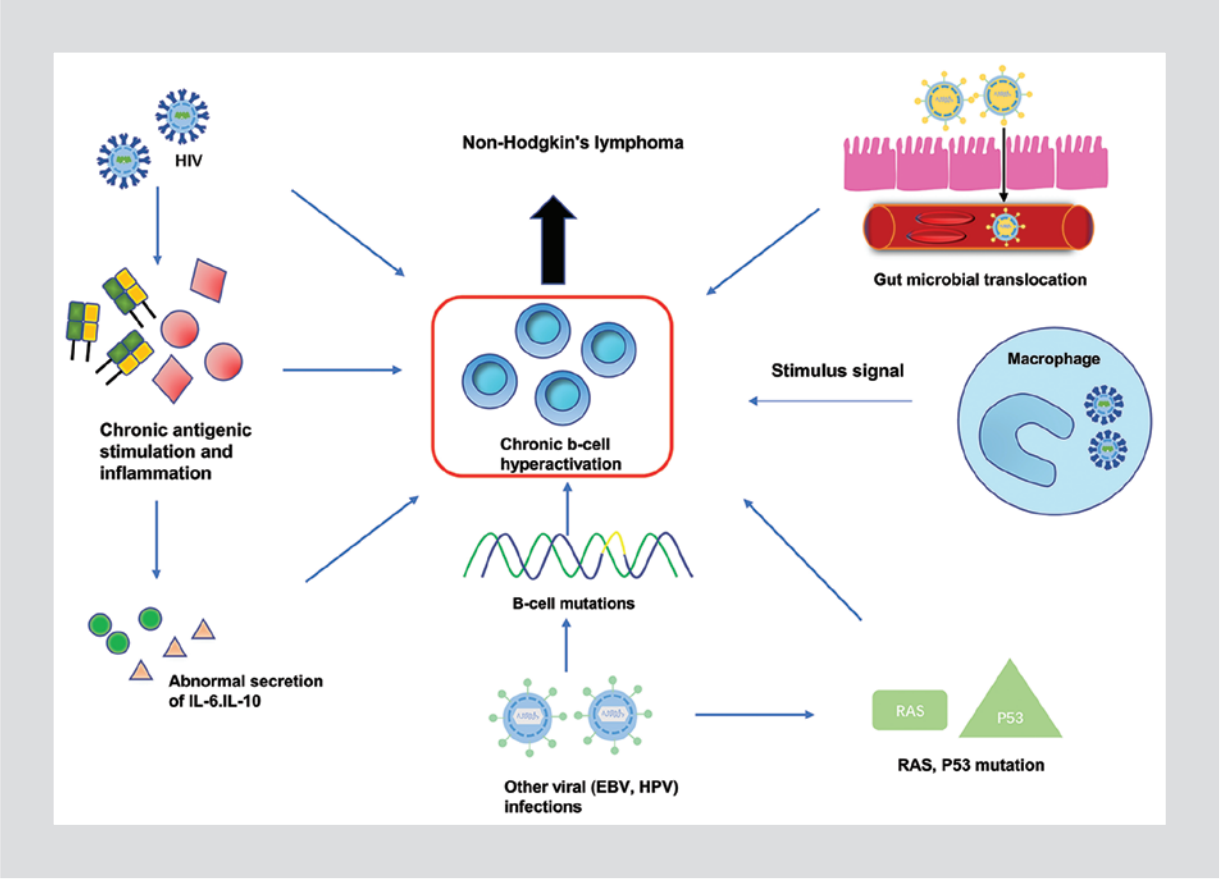

Figure 3. *The mechanism of chronic B-cell activation in HIV-1 infection. There are several mechanisms of chronic B-cell activation in HIV-1 infection. First, chronic antigenic stimulation and inflammation triggered by HIV infection may lead to dysregulated B-lymphocyte proliferation. In addition, abnormal secretion of cytokines such as IL-6 and IL-10 by HIV-1 promotes B-cell growth. Second, chronic antigenic stimulation of B cells by HIV itself may promote excessive activation and transformation of B cells. Third, chronic stimulation by other viral infections (including EBV, HPV, and HCV) may lead to mutations in B cells, as well as mutations in Ras and p53 genes. Fourth, macrophages provide stimulatory signals to B cells leading to B cell activation and malignant growth. Finally, leakage of bacterial components and products from the gut into the bloodstream (microbial translocation) is thought to be a potential cause of chronic immune activation in HIV infection. These factors in combination lead to continuous stimulation of B cells. Chronic polyclonal B-cell activation may eventually lead to the development of AIDS-related non-HL.*

production of ROS[40]. The effect of reverse transcription-induced ROS production on the growth and metastasis of 4T1luc2 cells, the mouse breast adenocarcinoma cells, was studied *in vitro* and *in vivo*[41]. The cells were made to express a panel of HIV-1 RT variants, and stable expression of RT in these cells was found leading to increased production of ROS that even exceeded the level observed in parental tumor cells. RT-expressing cells showed an enhanced migration activity and were transformed into a mesenchymal phenotype with increased expression of the transcription factors Twist and snail that coordinate as epithelial-mesenchymal transition (EMT)[40]. In syngeneic immunocompetent mice, these properties of RT-expressing cells lead to an enhanced tumor growth and metastatic activity. At the same time, HIV-1 infection can block the expression of NADH: ubiquinone oxidoreductase subunit A6 (NDUFA6) protein of the complex I subunit on the mitochondrial membrane, thereby directly reducing the activity of complex I[42]. Inhibition of complex I in turn increased the production of ROS. ROS can then activate nuclear factor kappa-B (NF-κB) and upregulate the expression of HIV-1 viral genes through HIV-1 long terminal repeats[43].

A recent study suggests that HIV is associated with an increased prevalence of clonal hematopoiesis of indeterminate potential (CHIP). CHIP is a recently recognized risk factor for hematologic malignancies. It is not entirely clear what causes the increased

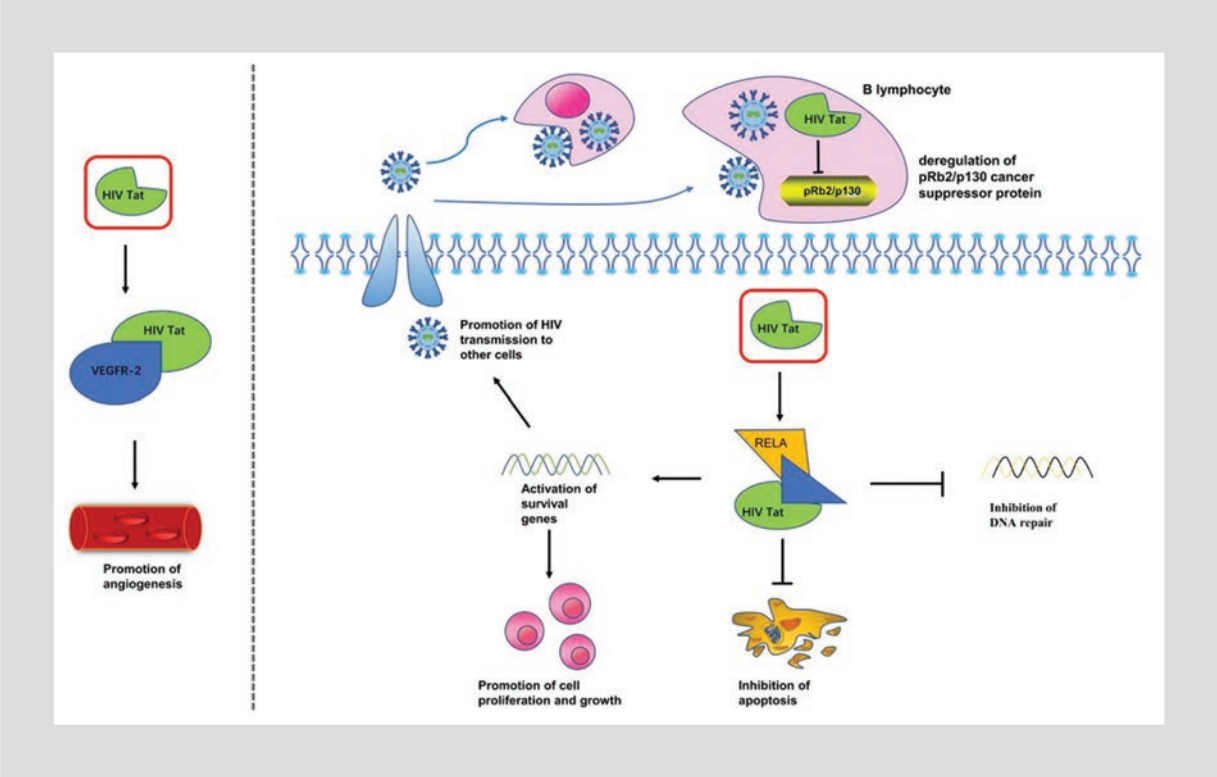

Figure 4. *The mechanism how HIV Tat promotes tumorigenesis. HIV Tat interacts with AKT1 and RELA (part of NF-kB). On the one hand, this interaction inhibits cell apoptosis and DNA repair. On the other hand, it activates survival genes to help HIV spread between cells and promote cell growth. In addition, Tat binds to VEGFR-2 due to its electronic property and promotes angiogenesis. Tat also interacts with and enters B lymphocytes causing dysfunction of pRb2/p130 tumor suppressor protein in the cells.*

prevalence of CHIP in PLWH. One plausible reason is that HIV infection accelerates biological aging and leads to chronic low-grade inflammation, which provides a favorable microenvironment for the development of CHIP[44]. Another possible cause is the direct effect of ART. The real contribution of these factors to CHIP risk requires further studies. Another study showed that HIV infection led to a greater risk of myelodysplastic syndromes (MDS), which are precursors of myeloid malignancies[45]. There is evidence that inflammatory signals promote the development of MDS[46]. The inflammatory environment induced by HIV infection may favor the growth and development of MDS-initiating cells. It is worth of noting that CHIP has been shown to be associated with the development of MDS[47].

Direct action of HIV

More and more pieces of evidence show that HIV directly participates in the development of malignant tumors. The interference with the apoptotic pathway by HIV may be related to the pathogenesis of tumors. In some studies, Tat, the transactivator protein of HIV, has shown carcinogenic effects *in vitro* and *in vivo*. For example, Tat was proven contributing to the pathogenesis of HIV-related KS[48,49]. Transgenic expression of Tat in mice contributes to the formation of KS-like lesions[50]. Studies revealed that Tat affected the life cycle of KS-associated herpesvirus (KSHV) and promoted the development of HIV-related KS by inducing cell proliferation and pro-inflammatory gene expression. Besides, interaction between Tat and AKT serine/threonine kinase 1 (AKT1)/NF-κBp65 (RELA) inhibited apoptosis and DNA repair of mutated cells[51,52]. Activation of certain survival genes by NF-kB may not only help HIV spread but also inadvertently promote the growth and proliferation of cancerous cells. Studies also show that extracellular Tat can enter uninfected cells and trans-activate cellular genes such as tumor necrosis factor, interleukin (IL)-2 and IL-6[53]. Tat is positively charged and can bind negatively-charged molecules such as vascular endothelial growth factor receptor 2 (VEGFR-2), an angiogenetic factor. With this

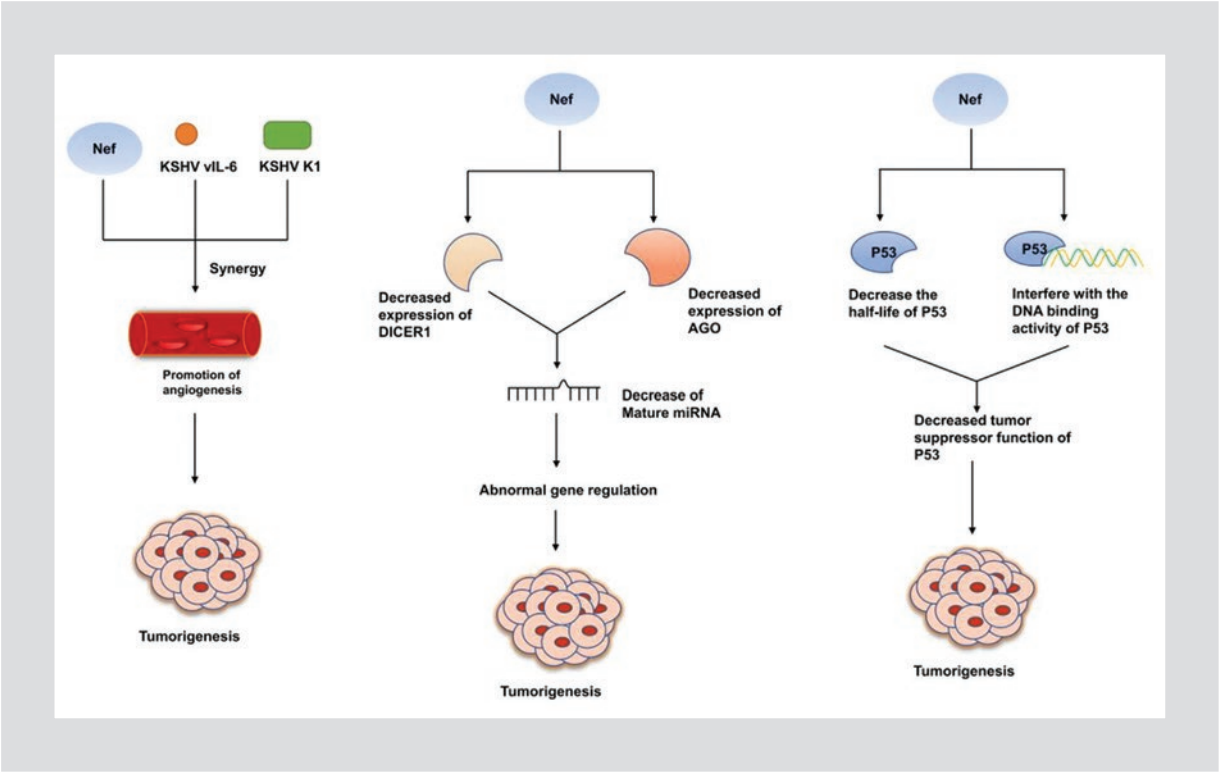

Figure 5. *The mechanism how HIV Nef promotes tumorigenesis. Nef promotes the occurrence of cancers through following mechanisms. KSHV vIL-6 and 2.117 mmNef act synergistically with KSHV K1 to promote blood vessel formation. Nef also caused a decrease in the expression of DICER1 and AGO (Argonaute), and subsequently a decrease in mature miRNA level in the cells. This dysregulation leads to abnormal gene regulation and promotes tumorigenesis. Besides, Nef inhibits the apoptotic function of P53 by reducing its half-life and interfering with its DNA binding activity.*

effect, Tat is likely to cause abnormal angiogenesis induced by KSHV during the formation of KS. Tat may also interact with and enter B lymphocytes leading to the deregulation of pRb2/p130 tumor suppressor protein (Fig. 4)[22,54].

HIV Nef was found having a similar effect as Tat: Nef promoted the angiogenesis and tumorigenesis of KSHV by manipulating the AKT signaling pathway[55]. *In vivo* experiments showed that Nef could promote KSHV Viral IL-6 (vIL-6)-induced angiogenesis and tumorigenesis, and KSHV vIL-6 and Nef cooperated with KSHV K1 (A unique transmembrane glycoprotein encoded by the KSHV genome) to promote the proliferation and microtubule production of human umbilical cord vascular endothelial cells[56,57].

Another study demonstrated that Nef could reprogram the initial stage during lung cancer development by manipulating cellular metabolism, cell survival and invasion, and angiogenesis. Nef also caused decreased expression of dicer 1 ribonuclease type III (DICER1) and Argonaute (AGO) and a subsequent decrease of mature miRNA in lung cells. Dicer, encoded by the DICER1 gene in the human body, is an RNase that plays an important role in RNA interference and belongs to type III RNase (RNase III). AGO protein is a key protein in RNA-mediated post-transcriptional gene regulation, providing an anchor site for miRNA to achieve the purpose of degrading target mRNA or inhibiting translation. miRNAs play a key role in cell signal transduction and homeostasis, and act like oncogenes or tumor suppressor genes[58]. Their dis-regulation promotes tumorigenesis. Besides, Nef inhibits the apoptotic function of P53 by reducing its half-life and interfering with its DNA binding activity. These studies indicate that Nef is directly involved in preventing cell death and promoting tumor progression (Fig. 5)[58].

It was recently discovered that variants of HIV p17 protein carried by certain HIV-infected patients with lymphoma have an enhanced B cell clonal activity. HIV p17 variants were secreted from infected cells and accumulated in lymphoid tissues, mainly in the germinal centers of lymph nodes. These variants may be the key microenvironmental factors that

promote the development of lymphoma[59,60]. Studies have shown that transgenic mice with genetically modified HIV-1 provirus that lacks a part of the gag-pol region and over-expresses p17, gp120, and Nef developed B-cell lymphoma. These all support the pathogenic role of abnormal expression of HIV proteins and B cell-stimulating factors in lymphoid tumorigenesis[61]. P17 produces a microenvironment that promotes lymph angiogenesis and the invasiveness of human triple-negative breast cancer cells[60]. The HIV-1 glycoprotein gp120 stimulates glycolysis[41]. Increased glycolysis is a feature of most tumors and supports unrestricted proliferation and invasion of tumor cells. Wherever it is expressed on viral particles, the surface of infected cells or as a virus-free soluble protein, gp120 promotes the proliferation, migration, and survival of tumor cells. Exposure of the oral keratinocytes from HIV-negative individuals to Tat or gp120 alone induces EMT. Also, introduction of Tat into human cervical cancer cells resulted in the up-regulation of HPV E6 but p53 level was reduced. HIV viral protein-experienced keratinocytes can be transformed by HPV 16 and then demonstrate the property of loss of cell adhesion and increased proliferation and migration[40,41]. These studies indicate that urogenital mucosal EMT driven by HIV protein may be one of the mechanisms by which HIV-1enhances the carcinogenic effect of HPV oncoproteins.

Conclusion

ART has transformed HIV infection from a fatal disease into a chronic disease, but at the same time makes cancer one of the leading causes of death in this patient population. Immunodeficiency is the earliest described mechanism, and it increases the incidence of various cancers. Furthermore, HIV shares the same transmission pathway as certain cancer-causing viruses, or because HIV infection suppresses host immunity, making PLWH vulnerable to viral infection. The oncogenic effects of viruses involve multiple pathways, including the apoptotic pathway and pathways that regulate the cell cycle or interfere with tumor-associated gene expression. Besides, chronic inflammation also greatly promotes carcinogenesis[31,62]. The inflammatory response induced by HIV may aggravate HBV or HCV associated liver diseases[31]. Microbial translocation from the intestine to the liver in HIV infection accelerates liver fibrosis[14]. Therefore, above factors may contribute to the development of hepatocellular carcinoma in HIV infection, especially in the context of HBV/HCV infection. Potential chronic antigen stimulation and inflammation is also thought to relate to dysregulated polyclonal or oligoclonal proliferation of B lymphocytes. Chronic polyclonal B cell activation is very important in the pathogenesis of cancer because chronic B cell activation contributes to not only the occurrence of HIV associated non-Hodgkins lymphoma but also B cell dysfunction and subsequent impaired *de novo* antibody response. It is reasonable to speculate that suppression of HIV may inhibit microbial translocation and subsequent immune activation despite that there is currently no research directly relating this to the risk of HIV associated non-Hodgkin lymphoma. Till now more and more evidences demonstrate that HIV directly participates in the development of malignancies, which probably is due to the direct action of HIV-encoded viral proteins such as P17 variants, Tat, Nef and gp120. These viral proteins promote tumorgenesis by regulating cell cycle, promoting cell growth and angiogenesis, inhibiting cell apoptosis and DNA repair and enhancing the clonal activity of B cells. Recently some studies evaluated whether P17 variants could be used as biomarkers to more accurately identify those HIV-infected individuals with an increased risk of lymphoma[62]. Therefore, identifying specific inhibitors that target the pathways manipulated by HIV proteins is promising. Related research is ongoing and progress has been made, but there are still important issues that need to be resolved before these inhibitors can be applied clinically.

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