HIV- and HERV-Cancer Paradigm

Animal retroviruses are known for their transforming potential, and this is also true for the ones hosted by humans, which have gathered expanding attention as one of the potent causative agents in various diseases, including specific cancer types. For instance, Human T Lymphotropic virus (HTLV) is a well-studied class of oncoviruses causing T cell leukemia, while human immunodeficiency virus (HIV) leads to acquired immunodeficiency syndrome (AIDS), which is linked to a series of defining cancers including Kaposi sarcoma, certain types of non-Hodgkin lymphoma, and cervical cancer. Of note, in addition to these "modern" exogenous retroviruses, our genome harbors a staggering number of human endogenous retroviruses (HERVs). HERVs are the genetic remnants of ancient retroviral germline infection of human ancestors and are typically silenced in normal tissues due to inactivating mutations and sequence loss. While some HERV elements have been appropriated and contribute to human physiological functions, others can be reactivated through epigenetic dysregulations to express retroviral elements and promote carcinogenesis. Conversely, HERV replication intermediates or protein products can also serve as intrinsic pathogen-associated molecular patterns that cause the immune system to interpret it as an exogenous infection, thereby stimulating immune responses against tumors. As such, HERVs have also been targeted as a potential internal strategy to sensitize tumor cells for promising immunotherapies. Further studies should help promote our understanding on the dynamic role of human retroviruses in cancer development including contribution from HIV and HERVs.

Keywords: human endogenous retroviruses ; human immunodeficiency virus ; carcinogenesis

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1. Introduction

Retroviruses are a large group of viruses that cause a wide range of diseases, including cancers. Accordingly, the well-described transforming nature of animal retroviruses led to their original definition as "RNA tumor viruses" [1]. Currently, there are two exogenous retroviruses affecting human health: human immunodeficiency virus (HIV) and human T lymphotropic virus (HTLV). While HTLV is a "classical" oncovirus, causing T cell leukemia as its main etiological manifestation, HIV infection is responsible for acquired immunodeficiency syndrome (AIDS), which is accompanied by a number of comorbidities, including increased incidence of different types of cancers [2].

Of note, in addition to the above exogenous retroviruses, the DNA of all vertebrate contains endogenous retroviruses (ERVs), which are ancient traces of past infections found as viral footprints in the genome of the various species. The ones found in humans, the human endogenous retroviruses (HERVs), represent as approximately 8% of the human genome and have been recently classified into 39 main groups [3]. These viral footprints are virus-associated sequences that closely resemble present-day retroviral (e.g., HIV) elements, including the 5' and 3' long terminal repeats (LTR), and the coding genes *gag*, *pro-pol*, and *env* [4]. However, their long-time persistence in the host genome has led to the accumulation of mutations as well as insertions and deletions, which have generally affected their capacity to produce infectious virions [5].

Viruses of the *Retroviridae* family typically contain two copies of positive-sense single-stranded RNA (ssRNA) genome at their core and are surrounded by host-derived lipid membrane inserted with the env gene-encoded glycoproteins (e.g., gp160 in the case of HIV, which is processed to yield the surface gp120 and the transmembrane gp41 [6]). The Env glycoproteins mediate the entry steps of HIV into the targeted host cells, whereas the viral enzymatic activities (reverse transcriptase (RT), RNase H, integrase (IN), and protease (PR)) encoded by the pro-pol gene are crucial to viral replication [6]. Retroviruses are characterized by their ability to perform reverse transcription of their ssRNA genome and integrating them into the host chromosomal DNA [7]. As such, ERVs are considered molecular remnants of ancient exogenous retroviruses resulted from their germ line infection and integration in vertebrate ancestors approximately over 100 million years ago [8].

2. HIV-Associated Cancers: Classification and Epidemiology

When the first clusters of AIDS epidemics were observed, at the beginning of the 1980s, the manifestations associated with immunodeficiency included Kaposi's sarcoma, aggressive B cell lymphomas, and invasive cervical cancer. These malignancies were commonly found in AIDS patients and thus became the "AIDS-defining" cancers when observed in HIV-infected individuals [9]. In addition to AIDS-defining cancers, a number of other malignancies are known to be associated to HIV infection, even if non-AIDS-defining, showing an increased incidence among HIV patients. These HIV-associated cancers include lung cancer, hepatocellular carcinoma, Hodgkin's lymphoma, oropharyngeal cancers, and anal and genital cancers [2]. The overall augmented cancer risk in HIV-infected individuals is driven by multiple factors. In most of these conditions, HIV does not have a direct transforming role, but the effects of its infection, especially on the host immune system, create a dysregulated environment triggering cancer development by both immunosuppression, which can aid in the immune evasion of oncoviruses and cancer cells, and chronic inflammation, which promotes cellular proliferation hence tumorigenesis [10][11]. Behavioral aspects of the HIV-infected individuals, such as the increased rate of co-exposure to oncoviruses in people with multiple sexual contacts or drug users, also contribute to the increased cancer risk [12].

Notably, the development of effective antiretroviral drugs (ARVs) has led to a significant reduction of AIDS-defining cancers [2]. In turn, the concomitant improvement of treated patients' survival has doubled the number of people living with AIDS, and a large proportion of them is currently in the age range that is associated with augmented cancer risk [13]. As a consequence of an aging HIV-infected population, the occurrence of both HIV-associated (non-AIDS-defining) cancers and common incidental cancers has increased, becoming the main cause of death in developed countries [2]. It is noteworthy that adolescents and young adults living with AIDS also have an increased risk of developing both AIDS-defining and non-AIDS-defining cancers compared to HIV-negative individuals of the same age, and their relatively low adherence to ARVs could aggravate the occurrence of malignancies [14].

3. AIDS-Defining HIV-Associated Cancers

The first cancer historically connected to AIDS' presence was Kaposi's sarcoma, characterized by lesions on the skin and other organs, including oral mucosa, gastrointestinal tract, lymph nodes, lungs, and bones [2]. Kaposi's sarcoma is caused by human herpesvirus 8, also known as Kaposi's sarcoma-associated herpesvirus (KSHV). KSHV does not require HIV infection to develop Kaposi's sarcoma, but the immune dysregulation induced by HIV affects the immunologic control of KSHV and other oncoviruses found in HIV patients, sustaining carcinogenesis. Accordingly, the risk of Kaposi's sarcoma in HIV patients is inversely related to their CD4+ T cell count, although a few patients with relatively high CD4+ T cell count still had persistent Kaposi's sarcoma [15]. The second group of AIDS-defining cancer is represented by aggressive B cell non-Hodgkin's lymphomas [2]. Of which, primary central nervous system lymphoma and plasmablastic lymphoma often consist of cells infected by Epstein Barr virus (EBV), while Burkitt's lymphoma and diffuse large B cell lymphoma are mainly negative for EBV [2]. Although the overall incidence of non-Hodgkin lymphomas in HIV patients showed a pronounced decrease with the advent of effective antiretroviral treatments, it still remains 10-fold higher as compared to uninfected population [16][17]. The third and last AIDS-defining malignancy is invasive cervical cancer, whose risk is increased in HIV-infected women, being associated with age but not with CD4+ T cell count [18]. Overall, almost all cervical cancers arise from human papilloma virus (HPV) oncogenesis, and the concomitant presence of HIV may augment its incidence by affecting the host immune response and thus preventing the clearance of HPV infection [11].

4. The Physiological Implications of HERV Elements

ERVs are viral footprints that are found in the host genomes. Over the time of evolution, integrated ERVs can be either lost or fixed (when the frequency of inserted ERV becomes 100% in the population), if the elements that are beneficial for the host, as a result of natural selection and random mutations [8]. Owing to their ability to integrate into the host genome, ERV sequences have important implication in host phenotypic effects that can have consequences in the context of physiological functions and diseases [19]. For example, the syncytins in humans, namely syncytin-1 encoded by a HERV-W provirus and syncytin-2 encoded by a HERV-FRD provirus, are thought to have been acquired by the primates many millions ago (~25 million years ago for syncytin-1 and >40 million years ago for syncytin-2) [20][21], and are essential for placental morphogenesis. It has also been proposed that the syncytins can have immunomodulatory functions including immunosuppression [22] and inhibition of Th1 cytokine production [23], possibly through the putative immunosuppressive domain in their transmembrane subunit. The overall effect is thought to contribute to the physiological maternal tolerance for the fetus during pregnancy [22][23][24]. Owing to their critical physiological roles in the placenta, this domestication and appropriation of the HERV Env exerts a positive selection for gene fixation or retention along the primate evolution, observing high degree of conservation and very limited human polymorphisms [24][25].

In addition, HERVs play a role in the regulation of human gene expression in several aspects. HERV elements serve as crucial regulatory factors for the pluripotency in embryonic stem cells [26] and are expressed at varied levels in normal human tissues [1][27] to facilitate tissue-specific gene expression. Furthermore, it is recently revealed that HERV-derived molecules modulate the innate immunity, which can elicit both positive antiviral protection against exogenous viruses and negative autoimmune and inflammatory disease-inducing effects [4]. These observations highlight the importance of HERV as a subject of study to unravel the genetic evolution of various species, and more intriguingly, for deciphering the pathophysiological development of illnesses and even be potentially explored as therapeutic targets for the treatment of many present day diseases.

5. HERV Activation and The Paradigm of HERV in Cancers

In most tissues, HERV are transcriptionally silenced by CpG methylation catalyzed by DNA methylase-1 [28]. The aberrant expression of HERVs have been found in a number of human diseases, such as cancers [29], autoimmune diseases [30], and neurological diseases [31], possibly suggesting their role in pathogenesis. Current literature suggests that HERV can be activated by a plethora of microenvironmental stimuli such as hormones, cytokines, epigenetic modifications or exogenous microorganisms [32]. Interestingly, recent studies suggest that several viral infections, such as retroviruses (HIV, HTLV-1), herpesviruses (EBV, herpes simplex virus type 1 [HSV-1], KSHV), HBV, and influenza virus, can transactivate HERV [33]. These findings might provide clues to the pathogenicity of certain viruses, including those that lead to long-term disease development such as autoimmune diseases and cancers.

In the case of cancer, a considerable level of early investigation has been focused on the oncogenic properties of retroviruses. Many studies attempted to illustrate the role of HERVs in cancer [34], as HERV elements and HERV-encoded proteins were found in a variety of cancers including melanoma, breast cancer, colorectal cancer, hepatobiliary cancers, prostate cancer, ovarian cancer, and germ cell tumors [32][35][36]. As such, HERV elements have been proposed to be potential biomarkers for cancers and could have implication for therapeutic intervention [36]. Although the average expression of HERV appears quite homogenous among different types of cancers [37], it is noteworthy that in some studies the overexpression of HERV was not found. For instance, in the analysis performed by Rooney et al., little overexpression of the "tumor-specific" HERVs (ERVH−5, ERVH48−1, and ERVE−4 in the study) was found in glioma and thyroid cancer [38]. In another study by Bergallo et al., while HERV-K *pol* was overexpressed in pediatric acute lymphoblastic leukemia (ALL) patients, the expression level was not significantly increased those with acute myeloid leukemia (AML) [39]. In contrast, Januszkiewicz-Lewandowska et al. demonstrated that HERV-K *env* was overexpressed in AML but not ALL [40]. In both studies, HERV-W *pol* and *env* were not found to be associated with either AML or ALL [39][40]. These examples suggest that HERV elements may not be overexpressed in all cancer types, and that different groups and different parts of HERV may be activated in specific malignancies.

In addition, it remains controversial whether the presence of HERV has a direct causative role or if it is simply a bystander effect of epigenetic changes such as hypomethylation of DNA and chromatin remodeling in the cancer cells, which could expose previously silent HERV LTRs [41]. In contrast, the continued investigation has also revealed that HERVs may contribute to host defense responses against cancer [42], implicating their presence as participants rather than mere bystanders. As a result, the precise role of HERV in cancer development remains to be fully clarified, and thus continuous studies and observations will help shed light to the evolving paradigm of HERV-cancer association.

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