HIV- and HERV-Cancer Paradigm

Subjects: Virology

Contributor: Ching-Hsuan Liu , Nicole Grandi , Lalitha Palanivelu , Enzo Tramontano , Liang-Tzung Lin

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.

human endogenous retroviruses | human immunodeficiency virus | carcinogenesis

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.

References

1. Grandi, N.; Tramontano, E. Type W Human Endogenous Retrovirus (HERV-W) Integrations and Their Mobilization by L1 Machinery: Contribution to the Human Transcriptome and Impact on the Host Physiopathology. Viruses 2017, 9, doi:10.3390/v9070162.
2. Yarchoan, R.; Uldrick, T.S. HIV-Associated Cancers and Related Diseases. New England Journal of Medicine 2018, 378, 1029-1041, doi:10.1056/NEJMra1615896.
3. Vargiu, L.; Rodriguez-Tome, P.; Sperber, G.O.; Cadeddu, M.; Grandi, N.; Blikstad, V.; Tramontano, E.; Blomberg, J. Classification and characterization of human endogenous retroviruses; mosaic forms are common. Retrovirology 2016, 13, 7, doi:10.1186/s12977-015-0232-y.
4. Grandi, N.; Tramontano, E. Human Endogenous Retroviruses Are Ancient Acquired Elements Still Shaping Innate Immune Responses. Front Immunol 2018, 9, doi:10.3389/fimmu.2018.02039.
5. Grandi, N.; Tramontano, E. HERV Envelope Proteins: Physiological Role and Pathogenic Potential in Cancer and Autoimmunity. Front Microbiol 2018, 9, 462, doi:10.3389/fmicb.2018.00462.
6. Votteler, J.; Schubert, U. Human Immunodeficiency Viruses: Molecular Biology. In Encyclopedia of Virology, 3 ed.; Mahy, B.W.J., van Regenmortel, M.H.V., Eds. Elsevier Ltd. : 2008; pp 517-525.
7. Sierra, S.; Kupfer, B.; Kaiser, R. Basics of the virology of HIV-1 and its replication. J Clin Virol 2005, 34, 233-244, doi:10.1016/j.jcv.2005.09.004.
8. Johnson, W.E. Origins and evolutionary consequences of ancient endogenous retroviruses. Nat Rev Microbiol 2019, 17, 355-370, doi:10.1038/s41579-019-0189-2.
9. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992, 41, 1-19.
10. Martinez-Maza, O.; Breen, E.C. B-cell activation and lymphoma in patients with HIV. Curr Opin Oncol 2002, 14, 528-532, doi:10.1097/00001622-200209000-00009.
11. Casper, C.; Crane, H.; Menon, M.; Money, D. HIV/AIDS Comorbidities: Impact on Cancer, Noncommunicable Diseases, and Reproductive Health. In Major Infectious Diseases, rd, Holmes, K.K., Bertozzi, S., Bloom, B.R., Jha, P., Eds. Washington (DC), 2017; 10.1596/978-1-4648-0524-0_ch3.
12. de Martel, C.; Shiels, M.S.; Franceschi, S.; Simard, E.P.; Vignat, J.; Hall, H.I.; Engels, E.A.; Plummer, M. Cancers attributable to infections among adults with HIV in the United States. AIDS

2015, 29, 2173-2181, doi:10.1097/QAD.0000000000000808.

13. Dubrow, R.; Silverberg, M.J.; Park, L.S.; Crothers, K.; Justice, A.C. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol 2012, 24, 506-516, doi:10.1097/CCO.0b013e328355e131.
14. Bohlius, J.; Foster, C.; Naidu, G.; Sengayi, M.; Turkova, A. Cancer in adolescents and young adults living with HIV. Curr Opin HIV AIDS 2018, 13, 196-203, doi:10.1097/COH.0000000000000460.
15. Maurer, T.; Ponte, M.; Leslie, K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. N Engl J Med 2007, 357, 1352-1353, doi:10.1056/NEJMc070508.
16. Robbins, H.A.; Shiels, M.S.; Pfeiffer, R.M.; Engels, E.A. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS 2014, 28, 881-890, doi:10.1097/QAD.0000000000000163.
17. van Leeuwen, M.T.; Vajdic, C.M.; Middleton, M.G.; McDonald, A.M.; Law, M.; Kaldor, J.M.; Grulich, A.E. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. AIDS 2009, 23, 2183-2190, doi:10.1097/QAD.0b013e328331d384.
18. Yanik, E.L.; Napravnik, S.; Cole, S.R.; Achenbach, C.J.; Gopal, S.; Olshan, A.; Dittmer, D.P.; Kitahata, M.M.; Mugavero, M.J.; Saag, M., et al. Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy. Clin Infect Dis 2013, 57, 756-764, doi:10.1093/cid/cit369.
19. Grandi, N.; Pisano, M.P.; Tramontano, E. The emerging field of human endogenous retroviruses: understanding their physiological role and contribution to diseases. Future Virology 2019, 14, 441-444, doi:10.2217/fvl-2019-0061.
20. Mallet, F.; Bouton, O.; Prudhomme, S.; Cheynet, V.; Oriol, G.; Bonnaud, B.; Lucotte, G.; Duret, L.; Mandrand, B. The endogenous retroviral locus ERVWE1 is a bona fide gene involved in hominoid placental physiology. Proc Natl Acad Sci U S A 2004, 101, 1731-1736, doi:10.1073/pnas.0305763101.
21. Blaise, S.; de Parseval, N.; Benit, L.; Heidmann, T. Genomewide screening for fusogenic human endogenous retrovirus envelopes identifies syncytin 2, a gene conserved on primate evolution. Proc Natl Acad Sci U S A 2003, 100, 13013-13018, doi:10.1073/pnas.2132646100.
22. Mangeney, M.; Renard, M.; Schlecht-Louf, G.; Bouallaga, I.; Heidmann, O.; Letzelter, C.; Richaud, A.; Ducos, B.; Heidmann, T. Placental syncytins: Genetic disjunction between the fusogenic and immunosuppressive activity of retroviral envelope proteins. Proc Natl Acad Sci U S A 2007, 104, 20534-20539, doi:10.1073/pnas.0707873105.

23. Tolosa, J.M.; Schjenken, J.E.; Clifton, V.L.; Vargas, A.; Barbeau, B.; Lowry, P.; Maiti, K.; Smith, R. The endogenous retroviral envelope protein syncytin-1 inhibits LPS/PHA-stimulated cytokine responses in human blood and is sorted into placental exosomes. Placenta 2012, 33, 933-941, doi:10.1016/j.placenta.2012.08.004.

24. Lavialle, C.; Cornelis, G.; Dupressoir, A.; Esnault, C.; Heidmann, O.; Vernochet, C.; Heidmann, T. Paleovirology of 'syncytins', retroviral env genes exapted for a role in placentation. Philos Trans R Soc Lond B Biol Sci 2013, 368, 20120507, doi:10.1098/rstb.2012.0507.

25. Esnault, C.; Cornelis, G.; Heidmann, O.; Heidmann, T. Differential evolutionary fate of an ancestral primate endogenous retrovirus envelope gene, the EnvV syncytin, captured for a function in placentation. PLoS Genet 2013, 9, e1003400, doi:10.1371/journal.pgen.1003400.

26. Schlesinger, S.; Goff, S.P. Retroviral transcriptional regulation and embryonic stem cells: war and peace. Mol Cell Biol 2015, 35, 770-777, doi:10.1128/MCB.01293-14.

27. Seifarth, W.; Frank, O.; Zeilfelder, U.; Spiess, B.; Greenwood, A.D.; Hehlmann, R.; Leib-Mosch, C. Comprehensive analysis of human endogenous retrovirus transcriptional activity in human tissues with a retrovirus-specific microarray. J Virol 2005, 79, 341-352, doi:10.1128/JVI.79.1.341-352.2005.

28. Lavie, L.; Kitova, M.; Maldener, E.; Meese, E.; Mayer, J. CpG methylation directly regulates transcriptional activity of the human endogenous retrovirus family HERV-K(HML-2). J Virol 2005, 79, 876-883, doi:10.1128/JVI.79.2.876-883.2005.

29. Downey, R.F.; Sullivan, F.J.; Wang-Johanning, F.; Ambs, S.; Giles, F.J.; Glynn, S.A. Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? Int J Cancer 2015, 137, 1249-1257, doi:10.1002/ijc.29003.

30. Greenig, M. HERVs, immunity, and autoimmunity: understanding the connection. PeerJ 2019, 7, e6711, doi:10.7717/peerj.6711.

31. Kury, P.; Nath, A.; Creange, A.; Dolei, A.; Marche, P.; Gold, J.; Giovannoni, G.; Hartung, H.P.; Perron, H. Human Endogenous Retroviruses in Neurological Diseases. Trends Mol Med 2018, 24, 379-394, doi:10.1016/j.molmed.2018.02.007.

32. Matteucci, C.; Balestrieri, E.; Argaw-Denboba, A.; Sinibaldi-Vallebona, P. Human endogenous retroviruses role in cancer cell stemness. Semin Cancer Biol 2018, 53, 17-30, doi:10.1016/j.semcancer.2018.10.001.

33. Chen, J.; Foroozesh, M.; Qin, Z. Transactivation of human endogenous retroviruses by tumor viruses and their functions in virus-associated malignancies. Oncogenesis 2019, 8, 6, doi:10.1038/s41389-018-0114-y.

34. Zhang, M.; Liang, J.Q.; Zheng, S. Expressional activation and functional roles of human endogenous retroviruses in cancers. Rev Med Virol 2019, 29, e2025, doi:10.1002/rmv.2025.

35. Attermann, A.S.; Bjerregaard, A.M.; Saini, S.K.; Gronbaek, K.; Hadrup, S.R. Human endogenous retroviruses and their implication for immunotherapeutics of cancer. Ann Oncol 2018, 29, 2183-2191, doi:10.1093/annonc/mdy413.

36. Grabski, D.F.; Hu, Y.; Sharma, M.; Rasmussen, S.K. Close to the Bedside: A Systematic Review of Endogenous Retroviruses and Their Impact in Oncology. J Surg Res 2019, 240, 145-155, doi:10.1016/j.jss.2019.02.009.

37. Smith, C.C.; Beckermann, K.E.; Bortone, D.S.; De Cubas, A.A.; Bixby, L.M.; Lee, S.J.; Panda, A.; Ganesan, S.; Bhanot, G.; Wallen, E.M., et al. Endogenous retroviral signatures predict immunotherapy response in clear cell renal cell carcinoma. J Clin Invest 2018, 128, 4804-4820, doi:10.1172/JCI121476.

38. Rooney, M.S.; Shukla, S.A.; Wu, C.J.; Getz, G.; Hacohen, N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell 2015, 160, 48-61, doi:10.1016/j.cell.2014.12.033.

39. Bergallo, M.; Montanari, P.; Mareschi, K.; Merlino, C.; Berger, M.; Bini, I.; Dapra, V.; Galliano, I.; Fagioli, F. Expression of the pol gene of human endogenous retroviruses HERV-K and -W in leukemia patients. Arch Virol 2017, 162, 3639-3644, doi:10.1007/s00705-017-3526-7.

40. Januszkiewicz-Lewandowska, D.; Nowicka, K.; Rembowska, J.; Fichna, M.; Zurawek, M.; Derwich, K.; Nowak, J. Env gene expression of human endogenous retrovirus-k and human endogenous retrovirus-w in childhood acute leukemia cells. Acta Haematol 2013, 129, 232-237, doi:10.1159/000345407.

41. Kassiotis, G.; Stoye, J.P. Making a virtue of necessity: the pleiotropic role of human endogenous retroviruses in cancer. Philos Trans R Soc Lond B Biol Sci 2017, 372, doi:10.1098/rstb.2016.0277.

42. Bannert, N.; Hofmann, H.; Block, A.; Hohn, O. HERVs New Role in Cancer: From Accused Perpetrators to Cheerful Protectors. Front Microbiol 2018, 9, 178, doi:10.3389/fmicb.2018.00178.