International Journal of Oncology Research
www.oncologyjournal.in
Online ISSN: 2664-6668, Print ISSN: 2664-665X
Received: 26-02-2022, Accepted: 13-03-2022, Published: 28-03-2022
Volume 2, Issue 1, 2022, Page No. 15-20

Oncogenic virus associated with human cancer: A review

Muhammad Ali[1*], Shamsu I Abdullahi[1], Gambo S[1], Khaleel ZI[2]
[1] Department of Microbiology, Federal University Gusau, Nigeria
[2] Department of Science Lab Technology, School of Technology, Kano State Polytechnics, Nigeria

DOI: https://doi.org/10.33545/2664665X.2022.v2.i1a.8

Abstract
In addition to chemicals and radiation, another source of mutation is viruses. Viruses are very small 'organisms' that can infect the cells of other animals or plants. However, the diversity and complexity of oncogenic mechanisms raises new questions as to the mechanistic role of viruses in cancer. Classical viral oncogenes have been identified for all tumor-associated viruses. To date, seven viruses; Epstein - Barr virus (EBV), Kaposi's Sarcoma Herpesvirus (KSHV), high-risk Human papilloma viruses (HPV), Merkel Cell Polyomavirus (MCPV), Hepatitis B Viruses (HBV), Hepatitis C Viruses (HCV) and Human T-Lymphotropic Virus type 1 (HTLV1)-have been consistently linked to different types of human cancer, and infections are estimated to account for up to 20% of all cancer cases worldwide. Viral oncogenic mechanisms generally include: generation of genomic instability, increase in the rate of cell proliferation, resistance to apoptosis, alterations in DNA repair mechanisms and cell polarity changes, which often coexist with evasion mechanisms of the antiviral immune response. Viral agents also indirectly contribute to the development of cancer mainly through immunosuppression or chronic inflammation, but also through chronic antigenic stimulation. The paper was aimed to review the oncogenic viruses associated with cancer in human as well as the molecular mechanisms by which the viruses induce cellular transformation and their associated cancers.

Keywords: cancer, human, oncogenic virus

Introduction
Viruses have well-established causal roles in numerous human and animal cancers, collectively responsible for almost one fifth of all cancers [1, 2]. Viral associated cancers are a special case of cancer biology and virology. To date, there are seven human viruses with strong epidemiological links to human cancers. These include members of the high-risk human papillomavirus (HPVs), hepatitis viruses B and C (HBV and HCV), human gammaherpes viruses (HHV4/Epstein-Barr Virus (EBV) and HHV8/Kaposi's Sarcoma-Associated Herpesvirus (KSHV), Merkel cell polyomavirus (MCPyV), and human T-cell leukemia virus I (HTLV-1). These oncoviruses represent members of vastly different families of virus, including DNA, RNA and retroviridae.
Despite this species diversity, these oncoviruses are thought to share common features that enable them to drive cancer. Oncoviruses usurp key cellular pathways important for the control of cell growth and metabolism. However, many non-cancer-causing viruses perturb these pathways and have similar viral-host interactions. Consequently, it is not fully understood what features confer viruses with oncogenic potential in human populations. Oncogenic viruses perturb numerous cellular pathways described as the hallmarks of cancers [3, 4]. As expected, viral associated cancer pathways can be readily superimposed on these cancer hallmarks [5]. And while the pathways of viral carcinogenesis are ultimately cellular, viruses do provide foreign genomes and gene products that create new interactions and pathways for oncogenesis. Most known oncogenic viruses of humans use DNA as their genomic material. Research over the past quarter century has revealed that their oncogenicity results largely from direct interference with barriers to oncogenesis. In contrast to viruses that have been accepted causes of particular cancers, candidate viral causes tend to have fewer viral than cellular genomes in the tumours. These low viral loads have caused researchers to conclude that the associated viruses are not primary causes of the associated cancers. Consideration of differential survival, reproduction and infiltration of cells in a tumour suggest, however, that viral loads could be low even when viruses are primary causes of cancer [5].

General Principles of Viral Oncogenic Mechanisms
Oncogenic viruses generally maintain chronic infections in which there is not or little production of viral particles, and that last for the whole life of the infected individual. These mechanisms of viral persistency and/or latency are biologically compatible with the carcinogenic process, because they avoid cell death most common in acute lytic infections, while maintaining the infectious agent hidden from the immune system. Viral persistence in the host is achieved by integrating the viral genome into the cell genome or by expressing viral proteins that equally segregate the viral genome into daughter cells during cell partitioning. Both mechanisms ensure that the virus is not lost during cellular replication. Viral persistence is usually characterized by expression of proteins that control cell death and proliferation; in this manner, oncogenic viruses nurture

infection of a controlled number of cells establishing a balance between virus and host, preserving the integrity of both. Cell transformation is probably not an evolutionary viral strategy, but rather a biological accident that rarely occurs in the virus-host interaction. Cancer leads to the death of the host, and thus, it also represents the end of the virus. The existence of viral oncogenes is explained as part of the viral persistence mechanisms, which only under altered conditions may lead to cancer. All virus-associated tumors result from the cooperation of various events, involving more than persistent infection and viral transformation mechanisms. Additional oncogenic hits are necessary for full-blown transformation. The occurrence of mutations impairing expression and function of viral and/or cellular oncogenes is necessary in the carcinogenic process, in line with that, an increased mutation rate of infected over normal cells is frequently observed [6, 7]. In this scenario, latently infected cells by oncogenic viruses might be more susceptible targets of additional oncogenic hits; e.g., due to smoking, a diet scarce in fruits and vegetables or/and increased exposure to environmental oncogenic agents. All these insults, plus the host genetic component driving inflammatory responses triggered by the infection itself result in cell transformation and cancer development.

Infectious agents can contribute to carcinogenesis by direct and/or indirect mechanisms. The direct-acting carcinogenic agents are generally found in a monoclonal form within the tumor cells. These agents help to keep the tumor phenotype through expression of either viral or cellular oncogenes [8]. Retroviruses, whose replication cycle requires the integration of the viral genome into the host genome, commonly transform because integration deregulates expression of cellular oncogenes or tumor suppressor genes. On the other hand, EBV is an example of a virus that does not need to integrate and transforms through expression of its own oncogenes

The indirect transforming viruses are not conditioned to exist within the cell that forms the tumor. These agents act through two main mechanisms:

1. Triggering chronic inflammation and oxidative stress that persistently damage local tissues; and
2. By producing immunosuppression that reduces or eliminates anti-tumor immune surveillance mechanisms.

Among the most documented viral agents belonging to the first group are HBV and HCV; chronic inflammation produced by persistent infection associated with any of these viruses is a major risk to develop hepatocellular carcinoma (HCC) [9, 10]. On the other hand, HIV belongs to the second group; patients with non-controlled infection and low T cell counts frequently develop lymphomas associated with EBV or KSV infection [11]

Human Oncogenic Viruses and Associated Cancers

1. Epstein - Barr virus (EBV)

EBV is associated is with lymphoproliferative disease, most commonly Burkitt's lymphoma. There is increasing evidence EBV is also associated with Hodgkin lymphoma. It's estimated that more than 90% of the World population is infected with EBV. EBV is responsible for infectious mononucleosis (the 'kissing disease'). The mechanism of transmission of EBV is generally unknown but possibly through saliva [12, 13]. EBV Infection usually begins in the epithelial cells of the oropharynx, posterior nasopharynx and parathyroid glands. From there EBV infects B cells and persistent infection is established. Almost all cases of EBV infection are controlled by the immune system and infected individuals are asymptomatic (have no symptoms of infection). B cell Infection is necessary for EBV mediated carcinogenesis [13]. Only a small percentage of infections lead to cancer, most cases arising in immune-compromised or transplanted individuals. These patients are especially susceptible because they lack sufficient immune function to inhibit the growth of infected B cells. EBV-mediated carcinogenesis is most likely caused by the actions of viral gene products [12]. Two proteins in particular are thought to play a major role in B cell immortalization; latent membrane proteins (LMP's) and EBV nuclear antigen (EBNA's). LMP1 is inserted into the host cell membrane and acts as an activated growth factor receptor, resulting in unregulated growth. EBNA's affect the cell in many different ways; one pathway leads to altered activity of tumor suppressors including Rb, p53, and Arf [12, 13].

2. Human Herpesvirus [Kaposi's Sarcoma Herpesvirus] (KSHV)

Human Herpesvirus is associated with Kaposi's Sarcoma (KS), a type of cancer that affects the skin and soft organs. HHV8 is also associated with several blood disorders. It is uncommon in most of the world, only 1-5% of people in North America and Northern Europe are infected. Mediterranean populations have a higher infection rate (5-20%) and Sub-Saharan Africa has the highest rate (>60%). In the U.S., gay men also have a higher infection rate (~40%). HHV8 is most commonly spread through sexual contact and via saliva. Transmission also may occur via organ transplantation or blood transfusion. HHV8 infects B cells, epithelial cells, endothelial cells and possibly monocytes. HHV8 infection is high in populations with high incidence of KS and low in populations with low incidence of KS. HHV8 DNA is found in all cases of KS, but infection is not enough to cause cancer. The exact method by which HH8V induces cancer is still under investigation. KS probably starts as an inflammatory process to which circulating cells (including HHV8 infected cells) are recruited, leading to further inflammation, tissue damage, and viral infection. HHV8 then establishes a persistent infection which may send signals promoting angiogenesis and inflammation. This cycle may ultimately lead to tumor development. Untreated AIDS confers a 20,000 fold higher risk of developing KS, but other than immunosuppression the role of AIDS is generally unknown [12, 14].

3. High-Risk Papillomaviruses

Human papilloma viruses belong to the *Papillomaviridae* family; they contain a double-strand DNA genome of approximately 8000 bp and are not enveloped viruses. More than 100 members of this family have been described and from them, more than a dozen (types 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 62, 66 and 68) have been classified as high-risk due to their epidemiological association with cervical and other cancers [15]. HPV subtypes 16 and 18 are the most frequently found in tumors; the first is mainly associated with invasive cervical cancer and the second is the most frequent in squamous cell carcinoma [16, 17]. Low-risk HPVs generally cause benign lesions, such as warts [18]. HPV is transmitted by skin contact, including genital contact during sexual intercourse; thus HPV infection in the genital area tents to be common in sexually active persons. Infection is generally controlled by the immune system and only in a low number of people, HPV persists, increasing the risk to develop epithelial lesions [19]. Viral persistence seems to be greatly helped by the inability of infected cells to present antigenic epitopes to adaptive immune cells, which is common in individuals with alterations in the HLA (Human Leucocyte Antigen) antigen presentation pathway [20].

The neoplastic progression involves a series of histological changes that have been stratified in clinical stages, which correlate with differential expression of viral oncogenes and accumulation of mutations in the host genome. The main oncogenic proteins are E6 and E7, which are required since the first lesions and are necessary for the maintenance of the malignant phenotype. HPV is usually not integrated into the host genomic DNA, and E2 negatively regulates the expression of E6 and E7. An important event in the oncogenic process is the integration of the viral genome, a step usually resulting in loss of E2 and over-expression of E6 and E7 [21]. Increased expression of E6 and E7 correlates with progression to high grade lesions and eventually to carcinoma *in situ* [19].

4. Merkel Cell Polyomavirus

Polyomaviruses are non-enveloped viruses with a circular, double-stranded DNA of approximately 5000 bp. The members of this family are present in all regions of the world infecting several species. Historically, it was considered that only JCV and BKV polyomaviruses infected humans, but next generation sequencing techniques have enabled the identification of at least nine other members in humans, among them MCPV. MCPV was identified in 2008 in an aggressive skin cancer denominated Merkel cell carcinoma (MCC) [22]. Virtually the whole adult population worldwide is infected by MCPV. Evidence supporting the participation of this agent in MCC carcinogenesis includes the presence of MCPV genomes in about 80% of the tumors but not in healthy tissue, and the clonal integration of the viral genome [22-25]. MCPV oncogenic transformation may result from loss of immune surveillance, as MCC mainly occurs in immunosuppressed individuals. MCC was a very rare cancer before the AIDS pandemia, and today, there are around 1700 new cases per year in the US [26, 27]. The MCPV genome is inserted into the host genome during viral carcinogenesis. Integration is characterized by preserving the viral induced cell proliferation functions while abrogating viral replication; the latter probably due to deletion of some of the viral T antigen gene regions [28, 29].

Viral integration also favors host resistance to cell death promoting viral persistence in a latent state [30]. This is a significant difference between the presence of the virus in MCC and in non-tumor tissue. Due to the recent discovery of MCPV, we still do not understand the function of viral proteins. However, some viral proteins present homology in functional domains with tumorigenic polyomaviruses from non-human species. For example, like SV40 MCPV T antigens are generated by differential splicing to produce large T and small T antigens [31]. The large T antigen presents the structural motif that inactivates pRb (LXCXE) [32], and the T antigen is generally expressed in MCC, and even in its truncated form it maintains intact the pRb-inactivating domain [33].

5. Hepatitis B Virus

The *Hepadnaviridae* family groups a series of viruses that cause liver disease in animals, with Hepatitis B virus (HBV) infecting humans. HBV is an enveloped virus with an approximate 3.2 Kb genome of a partially double stranded DNA chain and a single stranded fragment. HBV replicates through an intermediary RNA via a viral reverse transcriptase. The main target of infection by HBV is the hepatocyte and infection can occur through vertical or horizontal transmission starting in the first years of life or during adulthood [34]. Chronic infection by HBV is one of the main causes of hepatocellular carcinoma (HCC). The carcinogenesis process triggered by HBV is complex, involving direct and indirect mechanisms with the latter being driven by chronic inflammation [35]. Direct mechanisms such as expression of viral oncogenes and insertional mutagenesis have also been documented [36]. HBV X (HBx) is the main oncogenic viral protein. HBx is a viral replication protein that participates in transcription and DNA repair through which it regulates cell cycle, apoptosis and genomic instability [37]. Furthermore, HBx transgenic mice develop liver carcinomas [38].

6. Hepatitis C Virus

Hepatitis C virus (HCV) is a member of the *Flaviviridae* family; there are at least six genotypes that are regionally distributed and divided into subtypes [39]. The HCV genome consists of a single strand RNA of positive polarity of approximately 9600 nucleotides from which a polyprotein is translated from a unique open reading frame and later subdivided into different viral polypeptides by viral proteases [40]. HCV infects hepatocytes causing an acute infection that may turn chronic when the immune system cannot eliminate it. In

those cases, the carrier may progress to hepatitis, cirrhosis and eventually to HCC [40]. It is estimated that more than 170 million persons worldwide are infected by HCV from which about 40% will develop some form of liver disease and 1%–4% HCC [41]. Transmission commonly occurs through blood and infected blood products.
Direct and indirect transforming mechanisms have also been described for HCV. The viral oncoprotein Core is the only viral product that in transgenic mice promotes the appearance of HCC [42]. Core is the main trigger of steatosis, an abnormal retention of lipids within the hepatocyte, and oxidative stress leading to chronic liver damage and HCC [43]. Different functions have been attributed to this protein, including altered cellular gene transcription, cell proliferation and cell death. For instance, Core expression correlates with changes in the activity of bona fide cellular tumor suppressors and oncogenes, and also of intermediaries of MAP kinases, NFκB and β-catenin signaling pathways [44]. Core protein regulates ROS production by inducing nitric oxide synthase (iNOS) which activates cyclooxygenase-2 (COX-2), importantly contributing with oxidative stress [45]. iNOS andCOX-2 are also important components of the inflammatory pathway leading to cancer [46, 47]. Core localizes in the mitochondria where it regulates levels of the mitochondrial chaperone prohibitin; it is proposed that altered binding of prohibitin and cytochrome c oxidase results in increased oxidative stress that favors DNA damage [48]. Taken together all these data has contributed to the formation of a model in which accelerated cell division by the inhibition of p53, pRb and other cell proteins in the presence of DNA damage by oxidative stress and the inflammatory response leads to the development of HCC.

7. Human T-Lymphotropic Virus Type 1

The *Retroviridae* family groups several viruses with two copies of a positive sense single stranded RNA genome that is retro-transcribed to DNA and integrated into the host cell genome. Retroviruses are classified as simple and complex. Simple retroviruses encode *gag*, *pol* and *env* genes from which structural proteins are expressed, plus other proteins involved in viral replication and integration. Complex viruses encode additional regulatory genes besides the mentioned above. HTLV1 is a potent direct carcinogenic agent that has been associated with a spectrum of lymphoproliferative diseases collectively referred as adult T-cells leukemia/lymphoma (ATL) [49]. HTLV1 is endemic of Japan, the Western African coast, Central America and the Caribbean, with 15–25 million people infected worldwide [50]. There are three demonstrated ways of transmission for HTLV1: sexual contact, intravenous and breast feeding. The virus infects T- and Blymphocytes and dendritic cells *in vivo*. Although, the main retroviral mechanism of transformation is by insertional mutagenesis, HTLV1 is a complex retrovirus whose genome also encodes the Tax oncoprotein. Tax has the ability to immortalize cells *in vitro* and its enforced expression in transgenic mice results in development of leukemia/lymphoma [51]. Tax is a transcriptional activator/repressor capable of modulating expression of multiple cellular genes and it also directly interacts with a plethora of cellular proteins. Tax principal mechanism of transformation is related to reprogramming cell cycle and inhibition of DNA repair [52]. Tax induces NFκB activity, which stimulates the expression of cytokines and their receptors, including those of IL-13, IL-15, IL-2, IL-2Rα and co-stimulatory surface receptors (OX40/OX40L) [53–55]. Importantly, this activity mimics the chronic inflammatory process critical in the oncogenic progression of many types of cancers. These molecules trigger T cell proliferation, which may help to amplify the pool of HTLV1 infected cells. Thus, contrary to other cancers in which the inflammatory process is mediated by immune cells in response to the oncogenic insult, in HTLV1 infection this is directly induced by Tax. Besides NFkB promoters, Tax also regulates expression of cellular transcriptional promoters through interaction with cyclic-AMP response element binding protein (CREB) and serum response factor (SRF) [52].

Conclusion

Viral infection is an indisputable causal factor for nearly 15-20% of all human cancers. However, the diversity and complexity of oncogenic mechanisms raises new questions as to the mechanistic role of viruses in cancer. Classical viral oncogenes have been identified for all tumor-associated viruses. To date, seven viruses namely; EBV, KSHV, high-risk HPV, MCPV, HBV, HCV and HTLV1- have been consistently linked to different types of human cancer, and infections are estimated to account for up to 20% of all cancer cases worldwide.

References

1. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer,2006:118:3030–44. doi: 10.1002/ijc.21731
2. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health,2020:8:e180–90. doi: 10.1016/S2214-109X(19)30488-7
3. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000; 100:57–70. doi: 10.1016/S0092-8674(00)81683-9
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell,2011:144:646–74. doi: 10.1016/j.cell.2011.02.013
5. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. Cell Host Microbe,2014:15:266–82. doi: 10.1016/j.chom.2014.02.011
6. Loeb LA, Springgate CF, Battula N. Errors in DNA replication as a basis of malignant changes. Cancer Res,1974:34:2311–2321.

7. Prindle MJ, Fox EJ, Loeb LA. The mutator phenotype in cancer: Molecular mechanisms and targeting strategies. Curr. Drug Targets,2010:11:1296–1303.
8. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat. Rev. Cancer,2010:10:878–889.
9. Coleman WB. Mechanisms of human hepatocarcinogenesis. Curr. Mol. Med,2003:3:573–588.
10. Zucman-Rossi J, Laurent-Puig P. Genetic diversity of hepatocellular carcinomas and its
11. potential impact on targeted therapies. Pharmacogenomics,2007:8:997–1003.
12. Chadburn A, Abdul-Nabi AM, Teruya BS, Lo AA. Lymphoid proliferations associated with human immunodeficiency virus infection. Arch. Pathol. Lab. Med,2013:137:360–370.
13. Boccardo E, Villa LL. Viral Origins of Human Cancer. Current Medicinal Chemistry,2007:24:2526-39.
14. Brady G, Macarthur GJ, Farrell PJ. Epstein-Barr virus and Burkitt lymphoma. Postgrad Med J,2008:84(993):372-7.
15. Ensoli B, Sgadari C, *et al*. Biology of Kaposi's sarcoma. European Journal of Cancer,2001:37:1251-1269.
16. Zur Hausen H. Papillomaviruses and cancer: From basic studies to clinical application. Nat. Rev. Cancer,2002:2:342–350.
17. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, *et al*. International Agency for Research on Cancer Multicenter Cervical Cancer Study, G. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N. Engl. J. Med,2003:348:518–527.
18. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: A meta-analysis. Br. J. Cancer,2003:88:63–73.
19. Chow LT, Broker TR. Human papillomavirus infections: Warts or cancer? Cold Spring Harbor Perspect. Biol,2013:5:10.1101/cshperspect.a012997.
20. Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: Unresolved issues. Nat. Rev. Cancer,2007:7:11–22.
21. Zur Hausen H. Papillomaviruses—To vaccination and beyond. Biochem. Biokhimiia,2008:73:498–503.
22. Ghittoni R, Accardi R, Hasan U, Gheit T, Sylla B, Tommasino M. The biological properties of E6 and E7 oncoproteins from human papillomaviruses. Virus Genes,2010:40:1–13.
23. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human merkel cell carcinoma. Science,2008:319:1096–1100.
24. Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. Mc polyomavirus is frequently present in merkel cell carcinoma of european patients. J. Investig. Dermatol,2009:129:248–250.
25. Carter JJ, Paulson KG, Wipf GC, Miranda D, Madeleine MM, Johnson LG, *et al*. Association of merkel cell polyomavirus-specific antibodies with merkel cell carcinoma. J. Natl. Cancer Inst,2009:101:1510–1522.
26. Duncavage EJ, Zehnbauer BA, Pfeifer JD. Prevalence of merkel cell polyomavirus in merkel cell carcinoma. Mod. Pathol,2009:22:516–521.
27. Agelli M, Clegg LX. Epidemiology of primary merkel cell carcinoma in the United States. J. Am. Acad. Dermatol,2003:49:832–841.
28. Hodgson NC. Merkel cell carcinoma: Changing incidence trends. J. Surg. Oncol,2005:89:1–4.
29. Kassem A, Schopflin A, Diaz C, Weyers W, Stickeler E, Werner M *et al*. Frequent detection of merkel cell polyomavirus in human merkel cell carcinomas and identification of a unique deletion in the vp1 gene. Cancer Res,2008:68:5009–5013.
30. Kwun HJ, Guastafierro A, Shuda M, Meinke G, Bohm A, Moore PS, Chang Y. The minimum replication origin of merkel cell polyomavirus has a unique large t-antigen loading architecture and requires small t-antigen expression for optimal replication. J. Virol,2009:83:12118–12128.
31. Moens U, van Ghelue M, Johannessen M. Oncogenic potentials of the human polyomavirus regulatory proteins. Cell. Mol. Life Sci,2007:64:1656–1678.
32. Shuda M, Arora R, Kwun HJ, Feng H, Sarid R, Fernandez-Figueras MT, *et al*. Human merkel cell polyomavirus infection i. Mcv t antigen expression in merkel cell carcinoma, lymphoid tissues and lymphoid tumors. Int. J. Cancer,2009:125:1243–1249.
33. Shuda M, Feng H, Kwun HJ, Rosen ST, Gjoerup O, Moore PS, Chang Y. T antigen mutations are a human tumor-specific signature for merkel cell polyomavirus. Proc. Natl. Acad. Sci. USA,2008:105:16272–16277.
34. Houben R, Adam C, Baeurle A, Hesbacher S, Grimm J, Angermeyer S, *et al*. An intact retinoblastoma protein-binding site in merkel cell polyomavirus large t antigen is required for promoting growth of merkel cell carcinoma cells. Int. J. Cancer,2012:130:847–856.
35. Kew MC. Epidemiology of chronic hepatitis b virus infection, hepatocellular carcinoma, and hepatitis b virus-induced hepatocellular carcinoma. Pathol.-Biol,2010:58:273–277.
36. Tarocchi M, Polvani S, Marroncini G, Galli A. Molecular mechanism of hepatitis b virusinduced hepatocarcinogenesis. World J. Gastroenterol,2014:20:11630–11640.
37. Sung WK, Zheng H, Li S, Chen R, Liu X, Li Y, *et al*. Genome-wide survey of recurrent hbv integration in hepatocellular carcinoma. Nat. Genet,2012:44:765–769.
38. Wen Y, Golubkov VS, Strongin AY, Jiang W, Reed JC. Interaction of hepatitis b viral oncoprotein with cellular target hbxip dysregulates centrosome dynamics and mitotic spindle formation. J. Biol. Chem,2008:283:2793–2803.

39. Kim CM, Koike K, Saito I, Miyamura T, Jay G. Hbx gene of hepatitis b virus induces liver cancer in transgenic mice. Nature,1991:351:317–320.
40. Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, Feinstone S, *et al*. Consensus proposals for a unified system of nomenclature of hepatitis c virus genotypes. Hepatology,2005:42:962–973.
41. Tang H, Grise H. Cellular and molecular biology of hcv infection and hepatitis. Clin. Sci,2009:117:49–65.
42. Morgan RL, Baack B, Smith BD, Yartel, A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis c virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. Ann. Intern. Med,2013:158:329–337.
43. Moriya K, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K, *et al*. The core protein of hepatitis c virus induces hepatocellular carcinoma in transgenic mice. Nat. Med,1998:4:1065–1067.
44. Moriya K, Yotsuyanagi H, Shintani Y, Fujie H, Ishibashi K, Matsuura Y, *et al*. Hepatitis c virus core protein induces hepatic steatosis in transgenic mice. J. Gen. Virol,1997:78(Pt 7):1527–1531.
45. Pei Y, Zhang T, Renault V, Zhang X. An overview of hepatocellular carcinoma study by omics-based methods. Acta Biochim. Biophys. Sin,2009:41:1–15.
46. Nunez O, Fernandez-Martinez A, Majano PL, Apolinario A, Gomez-Gonzalo M, Benedicto I, *et al*. Increased intrahepatic cyclooxygenase 2, matrix metalloproteinase 2, and matrix metalloproteinase 9 expression is associated with progressive liver disease in chronic hepatitis c virus infection: Role of viral core and ns5a proteins. Gut,2004:53:1665–1672.
47. Murakami A, Ohigashi H. Targeting nox, inos and cox-2 in inflammatory cells: Chemoprevention using food phytochemicals. Int. J. Cancer,2007:121:2357–2363.
48. Ohshima H, Tazawa H, Sylla BS, Sawa T. Prevention of human cancer by modulation of chronic inflammatory processes. Mutat. Res,2005:591:110–122.
49. Fujinaga H, Tsutsumi T, Yotsuyanagi H, Moriya K, Koike K. Hepatocarcinogenesis in hepatitis c: Hcv shrewdly exacerbates oxidative stress by modulating both production and scavenging of reactive oxygen species. Oncology,2011:81 (Suppl. S1):11–17.
50. Kannian P, Green PL. Human t lymphotropic virus type 1 (htlv-1): Molecular biology and oncogenesis. Viruses,2010:2:2037–2077.
51. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-i infection and associated diseases. Oncogene,2005:24:6058–6068.
52. Grassmann R, Dengler C, Muller-Fleckenstein I, Fleckenstein B, McGuire K, Dokhelar MC, *et al*. Transformation to continuous growth of primary human lymphocytes by human t-cell leukemia virus type i x-region genes transduced by a herpesvirus saimiri vector. Proc. Natl. Acad. Sci. USA,1989:86:3351–3355.
53. Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of tax protein in human t-cell leukemia virus type-i leukemogenicity. Retrovirology,2004:1:20.
54. Li XH, Gaynor RB. Mechanisms of nf-kappab activation by the htlv type 1 tax protein. AIDS Res. Hum. Retrovir,2000:16:1583–1590.
55. Harhaj EW, Harhaj NS, Grant C, Mostoller K, Alefantis T, Sun SC, Wigdahl B. Human t cell leukemia virus type i tax activates cd40 gene expression via the nf-kappa b pathway. Virology,2005:333:145–158.
56. Mori N, Fujii M, Cheng G, Ikeda S, Yamasaki Y, Yamada Y, *et al*. Human t-cell leukemia virus type i tax protein induces the expression of anti-apoptotic genebcl-xl in human t-cells through nuclear factor-kappab and c-amp responsive element binding protein pathways. Virus Genes,2001:22:279–287.