

Around the cancer, short description: viruses and viral microRNAs

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Cancer is a neoplastic disease of multifactorial origin; its development depends on the interaction of the organism's genes with the environment. Although some cancers are hereditary, the majority of tumors is of the sporadic type. Cancer caused by infectious agents such as bacteria, parasites, and viruses has been estimated to be 16.1%. Viruses cause different infections depending on the species of virus and the organ affected. Although viral infection can occur without or with symptoms, such infections can result in acute neurological disorders and/or the induction of cancerous processes. Virus-cell interactions produce different effects, from the undetectable, to disease, or to death, by causing alterations in the host cell membrane and in apoptosis. Oncoviruses use different strategies that contribute to cancer development. These strategies can involve genomic (genomes), proteomic (proteins; their functions and structures), and epigenetic [methylation, histones modifications, ncRNAs (small and large)] factors and can include interactions with cellular targets such as tumor-suppressor proteins p53 and Rb and alteration of the proto-oncogene/oncogene equilibrium. The viruses associated with cancer are EBV, KSHV, HPV, HBV, HCV, HTLV-1, SV40, JCV, BKV, and MCV, whereas HIV is considered an indirect carcinogen and HCMV, an oncomodulator. The role of MMTV/HMTV is controversial. The involvement of viruses in cancer-related events is very broad. Molecular tools are used not only to assess the involvement of genes, either over- or under- expressed, in the control of cell growth, tumor progression, and metastatic events, but also to evaluate the genes and proteins signatures in prognosis and therapeutics to treat the direct or indirect causal agents of diseases.

Keywords cancer; virus; viral microRNA; human microRNA.

1. Introduction

Cancer is a neoplastic disease of multifactorial origin; its development depends on the interaction of the organism's genes with the environment. Although some cancers are hereditary, the majority of tumors is of the sporadic type, i.e., they originate *de novo* from somatic genetic changes that are promoted by exposure to environmental carcinogens and/or infectious agents. Cancer caused by infectious agents such as bacteria, parasites, and viruses has been estimated to be 16.1% [1]. In 2008, about two million cancer cases were attributed to infections [1]. Currently, there are >5,000 known viruses [2]. Rous in 1911 [2] and Epstein and Barr in 1964 [2] were the first scientists to discover cancer-related viruses. Research on viruses employs various methodologies: detection of antigens, detection of antibodies, cell culture, electron microscopy, detection of nucleotide(s) (nt) sequence(s) by reverse transcription and/or end-point or real-time polymerase chain reaction, sequencing, genomics, bioinformatics, and systems biology.

Detection of a virus or its genetic sequence in a particular tumor is not sufficient to unambiguously prove the virus to be a causal factor in the genesis of the disease. However, fulfillment of Koch's postulates—guidelines for the evidence required to establish causality for a disease [3]—has proven difficult for the oncogenic viruses discovered to date. Broader epidemiological criteria for causality, proposed by Sir Austin Bradford-Hill, have become accepted; these provide helpful guidelines when assessing potential virus-cancer associations. Bradford-Hill's criteria for causation in disease are the following: 1) strength of association; 2) consistency of association; 3) specificity of association; 4) temporality; 5) biological gradient; 6) plausibility; 7) coherence; 8) experiment; and 9) analogy [4]. The viruses associated with cancer are mentioned listed in Table 1.

Viruses cause different infections depending on the species of virus and the organ affected. Although viral infection can occur without or with symptoms, such infections can result in acute neurological disorders and/or the induction of cancerous processes. Virus-cell interactions produce different effects, from the undetectable, to disease, to death by causing alterations in the host cell membrane and in apoptosis [5]. However, some viruses persist for long periods of time and apparently do not cause changes in the infected cell. Latency or pseudolateny is a characteristic of herpesviruses [6]; some members of this group produce cellular proliferation, but not malignancy, whereas others may trigger cancer [7]. Cellular processes, as apoptosis and cell cycle, are altered by products of oncogenic viruses [8]. Oncoviruses use different strategies that contribute to cancer development, including interactions with cellular targets such as tumor-suppressor proteins p53 and Rb or alteration of the proto-oncogene/oncogene equilibrium [8, 9].

Tumor viruses encode several abundant, functional, RNA molecules that are non-coding (ncRNAs). There is no direct correlation between expression of these RNA molecules during virus transformation and the resulting tumorigenesis. However, studies show that ncRNAs may have some functions related to virus latency, survival of the infected cell, and/or oncogenic potential. It is possible that tumor viruses may utilize ncRNAs (large and/or small) to

manipulate host-cell gene expression by down-regulation of host ncRNAs small (microRNAs) [10-13]. microRNAs about 18–23 nucleotides in length, have large-scale effects on the expression of a variety of genes at the transcriptional and translational level, through base pairing with its targeted mRNAs. Viral microRNAs may modulate tumorigenesis through various mechanisms during tumor virus infection, e.g. decrease tumor suppression genes expression or increase oncogenes expression.

Table 1 The viruses associated with cancer.

| Virus | Taxonomy | Genome | nt | Group ^a (IARC) | Cancer sites | Cancer |
|--------|------------------|--------------------|--------|--|---|---|
| EBV | Herpesviridae | dsDNA | 171832 | 1 | Nasopharynx, leukemia and/or lymphoma | BL, NPC, HD, GC |
| KSHV | Herpesviridae | dsDNA | 137969 | 1 | Endothelium, leukemia and/or lymphoma | KS, PEL, MCD |
| HPV | Papillomaviridae | dsDNA | 8000 | 1 (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) 2A (HPV 68) 2B (26, 53, 66, 67, 70, 73, 82, 5, 8, 30, 34, 69, 85, 97) | Uterus, cervix, anus, vulva, vagina, penis oral cavity, tonsil, pharynx | Cervical, oropharyngeal, anogenital, skin |
| HBV | Hepadnaviridae | dsDNA (partial) | 3215 | 1 | Liver and bile duct | HCC |
| HCV | Flavaviridae | ssRNA | 9646 | 1 | Liver and bile duct | HCC |
| HTLV-1 | Retroviridae | ssRNA >dsDNA | 8507 | 1 | Leukemia and/or lymphoma | ATL |
| HIV-1 | Retroviridae | ssRNA >dsDNA | 9181 | 1 (indirect) | Anus, endothelium, eye, leukemia and/or lymphoma | Unknown |
| MCV | Polyomaviridae | dsDNA | 5387 | 2A | | MCC |
| JCV | Polyomaviridae | dsDNA | 5130 | 2B | Brain | CRC, glioma, meduloblastoma |
| BKV | Polyomaviridae | dsDNA | 5153 | 2B | Prostate, brain | Prostate, brain |

^a Agents classified according to IARC (International Agency for Research on Cancer). Group 1: carcinogenic to humans; group 2A: probably carcinogenic to humans; group 2B: possibly carcinogenic to humans; group 3: not classifiable as to its carcinogenicity to humans; Group 4: probably not carcinogenic to humans.

Abbreviations: EBV, Epstein-Barr virus; HBV, human hepatitis B virus; HCV, human hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HTLV-1, human T-cell lymphoma virus type 1; KSHV, Kaposi's sarcoma-associated herpesvirus; JCV, JC virus; BKV, BK virus; MCV, MC virus; dsDNA, double-stranded deoxyribonucleic acid; ssRNA, single-stranded ribonucleic acid; nt, nucleotides.

2. Epstein Barr Virus

EBV or human herpes virus 4 (HHV-4) is one of most common viruses to be found in humans, with 95% of world's population and half of the world's infants being infected [14, Table 1]. The EBV genome exists in two different states—lytic and latent—in the host, but all phases of the EBV life cycle are associated with human diseases [13].

2.1. Viral microRNAs

EBV codes for 25 microRNAs: ebv-mir -BART1-22 and -BHRF1-1, 1-2, 1-3. The ebv-mir-BART3 has target-validated human genes: RAB13 (assembly and/or activity of tight junctions) and IPO7 (importin-7, nuclear protein); ebv-mir-BART16 has target-validated human genes: RAB13 and TOMM2 (mitochondrial translocase), and ebv-mir-BART6 has target-validated human gene: DICER1 (endoribonuclease, required for formation RNA-induced silencing complex, and cleaves double strands RNA to produce siRNAs) [15]. EBV strongly up-regulates microRNA-155 in Burkitt Lymphoma [16].

2.2. Transmission and Protection

Infection with EBV occurs by the oral transfer of saliva [17]. Ganciclovir and acyclovir are drugs used to treat EBV infection. Several pharmaceutical companies are working on the development of a vaccine.

3. Kaposi's Sarcoma-Associated Herpes Virus

Kaposi's sarcoma-associated herpesvirus, KSHV or HHV-8, is the second cancer-associated herpesvirus (Table 1). KSHV (100–150 nm in diameter) is enveloped by lipid; infect a wide variety of cell types. There are seven KSHV genes [LANA, v-cyclin D, vFLIP (K13), Kaposin (K12), vIRF2 (K11.5), vIRF3 (K10.5), and LAMP (K15)] associated with latency and tumorigenic potential; are involved in viral maintenance and disruption of the host immune response [7, 18, 19, 13].

3.1. Viral microRNAs

The microRNAs encoded by KSHV in primary effusion lymphoma revealed more than 2000 cellular mRNA targets [20]. Polymorphism in viral-encoded microRNAs has been described for viral-infected cell lines and for clinical samples [21]. In addition, KSHV encodes 12 pre-microRNA (kshv-mir K12-1-12), encoding 18 microRNAs which are generated from one transcript [22, 13]. The target validated human genes NFKB1A (inhibitor NFKB), MAF (transcriptional activator or repressor), LRRC8D (leucine-rich repeat containing eight family, member D), NHP2L1 (binds to the 5'-stem loop of U4 snRNA and may play a role in the late stage of spliceosome assembly), GEMIN8 (plays an essential role in spliceosome snRNP assembly), ORF50, BCLAF1 (transcriptional activator or repressor), BACH1 (transcriptional regulator, repressor or activator), BCUR1 (transcription factor), TM6SF1 (transmembrane protein), LDOC1 (inhibitor of the cell cycle kinase CDK2), MATR3 (matrix nuclear protein, may have a role in nuclear retention of defective RNAs) [15].

3.2. Transmission and Protection

KSHV, like genital herpes, is primarily a sexually transmitted virus, with saliva being one of the main routes of transmission [23]. A vaccine to prevent KSHV infection is not currently available.

4. Human Papilloma Virus

Human papilloma virus (HPV) infects epithelium (Table 1). The Papillomaviridae family contains 29 genera formed by 191 viral types, for which the nucleotide sequence of the L1 open-reading frame has at least 10% dissimilarity to any other papillomavirus type [23]; specifically, 153 viral types of HPV are documented [24,25]. HPV are classified epidemiologically as high risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) or low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108) types, depending on oncogenic capacity and association to cervical cancer [26, 27, 6]. The others viral types are not yet classified. Other malignant neoplasms are related to infection with high-risk HPV; such neoplasms include those of the vagina, vulva, penis, and anus and of the head and neck, especially the oropharynx [28; WHO, 2012].

The HPV genome is divided into three regions: long regulatory region (LCR); early region (E1, E2, E4-E7), and late regions (L1 and L2) [29]. The main transforming capacity of high-risk HPV types is due to oncoproteins E6 and E7.

4.1. Viral microRNAs

HPV-microRNAs have not been reported [30]. Moreover, several studies have shown that HPV modulates the expression of cellular microRNAs. Specifically, E5 HPV16 could modulate expression of microRNA -146a, -203, and -324-5p [31].

4.2. Transmission and Protection

HPV transmission typically occurs through direct skin-to-skin contact, including genital-to-genital contact. Vaccines have been developed. Gardasil® (Merck Sharp & Dohme, 2006) and Cervarix® (GlaxoSmithKline, 2007) were approved by the U.S. Food and Drug Administration (FDA).

5. Human Hepatitis B Virus

Blumberg discovered HBV in 1965. In 2011, the World Health Organization (WHO) reported that, worldwide, two billion persons were infected with HBV and 350 million have a chronic infection [32]. HBV, the smallest known viral genome (3215 nt), encodes several proteins from four genes (*P*, *S*, *X*, and *C*). It comprises ten genotypes (A to J), with each genotype differing from the others by more than 8% of its nucleotides sequence; subgenotypes and serological subtypes exist. HBV is the causative agent of the majority of hepatocellular carcinomas (HCC) [33, 34, Table 1].

5.1. Viral microRNAs

HBV-microRNAs have not been reported. However, it has been suggested that microRNA-18a acts like a potential non-invasive biomarker in HCC related to HBV [35].

5.2. Transmission and Protection

HBV can be transmitted by blood and blood products; saliva; cerebrospinal, peritoneal, pleural, pericardial, synovial, and amniotic fluids; and semen and vaginal secretions. Transmission mode includes mother-to-infant, child-to-child, unsafe injections, blood transfusions, and sexual contact. The HBV vaccine was the first vaccine against a virus carcinogen [36]. A number of HBV vaccines are available, including Engerix®-B (Glaxo SmithKline), Shanvac®-B (Shantha Biotech), and Genevac® BTM (Serum Institute).

6. Human Hepatitis C Virus

HCV (50 nm in diameter) is classified into 11 major genotypes (designated 1–11), many subtypes (designated a, b, c, etc.), and about 100 different strains (numbered 1, 2, 3, etc.), based on the heterogeneity of the genomic sequence. In 2011, WHO estimated that about 3% of the world's population has been infected with HCV and that there are more than 170 million chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer [37, 38]. HCV is unable to integrate into the host genome, and viral protein expression has a more critical function in hepatocarcinogenesis, a complex multistep process involving a number of genetic and epigenetic alterations. These include the pathways of Wnt/b-catenin, p53, pRb, Ras, mitogen-activated protein kinase (MAPK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase (PI3K)/Akt, Hedgehog, and growth factors, such as epidermal growth factor, and transforming growth factor- β (TGF- β) [37-39, Table 1].

6.1. Viral microRNAs

HCV-microRNAs have not been reported.

6.2. Transmission and Protection

HCV is primarily transmitted parentally. It has been confirmed that it is also transmitted through sexual contact, intravenous drug use, blood transfusions, and unsafe medical procedures. The cause of transmission remains unknown in 20% of cases [WHO, 2011].

There is no vaccine against HCV. IFN- α preparations are now a critical component in the treatment of chronic hepatitis C infection [40]. Two protease inhibitors of HCV, Victrelis™ (Merck Sharp & Dohme) and Incivek™ (Vertex Pharmaceuticals Inc.) have been approved by FDA for the treatment of chronic HCV infection [41, 42].

7. Human T-Cell Leukemia Virus Type 1

Poiesz (1980) discovered HTLV-1 in T-cell leukemia/lymphoma cell lines [43]. HTLV-1 (80–100 nm in diameter) is an enveloped virus that infects 20 million persons worldwide [44]; is directly associated with a neoplasm (Table 1). HTLV-1 can infect different types of cells; however, it induces transformation only in T cells. The transforming capacity of HTLV-1 is due to Tax protein [45, 13]. In areas endemic for HTLV-1 infection, adult T-cell leukemia/lymphoma (ATLL) is prevalent [45-48, 13]. It is unclear whether HTLV-1 integrates its genome into the host randomly [49, 50,

13]; thus, it is not possible to state whether the mechanism involved comprises insertional mutagenesis or alterations in cellular proto-oncogenes [45, 13].

7.1. Viral microRNAs

HTLV-microRNAs have not been reported.

7.2. Transmission and Protection

HTLV-1 can be transmitted by transfusion of infected blood, sexual intercourse, and by sharing contaminated needles. Some treatment options have been investigated, including Zidovudine® (GlaxoSmithKline) and Pralatrexate® solution (Allos Therapeutics, Inc.), both of which are directed toward the cancer rather than the virus itself [51].

8. Human Immunodeficiency Virus

In 2011, WHO reported that 34.2 million persons were infected with AIDS—30.7 millions adults and 3.4 millions of children. Human immunodeficiency viruses (HIV) -1 and -2 are classic indirect carcinogens: the immunosuppression induced by these infections produces an increased frequency of tumors caused by other viruses such as EBV, HPV, and KSHV [7, 52]. Once the HIV genome has been reverse-transcribed, it is integrated into the host genome and the viral protein integrase begins its function, causing activation of latent viruses or viruses produced by the host's replication and translation machinery [53].

8.1. Viral microRNAs

Several HIV-microRNAs have been reported: microRNA -H1, -TAR, -TAR-5p, -TAR-p, HAAMicroRNA, VmicroRNA 1-5, and -N367 [54].

8.2. Transmission and Protection

HIV can be transmitted from an infected person to another through transfusion of infected blood and the use of infected needles, semen, vaginal secretions, and breast milk. HIV can be suppressed by combination antiretroviral therapy (ART) consisting of three or more of the following antiretroviral (ARV) drugs: zidovudine®, lamivudine®, acabavir®, lopinavir®, ritonavir®, tenofovir®, emtricitabine®, rilpivirine®, elvitegravir®, or cobicistat®. ART does not cure HIV infection but controls viral replication within a person's body, thus allowing an individual's immune system to strengthen and regain the power to fight off infections [55].

9. Human Cytomegalovirus

HCMV or HHV-5 infects 50–100% of the population in the world [56, WHO 2011]. It can remain latent for long periods of time without producing symptoms in the host; however, some individuals develop mononucleosis and hepatitis. On evaluating the involvement of this virus in carcinogenesis, the term "oncomodulator" emerged, i.e., the HCMV present in tumor cells increases tumorigenicity [56]. Although not yet demonstrated, a number of genes within HCMV (*UL70*, *US29*, and *UL150*) could potentially be regulated by this antisense mechanism [57].

9.1. Viral microRNAs

The importance of microRNA targeting of antiviral responses is further supported by the observation that HCMV (also KSHV and EBV) microRNAs, target the host cell ligands MIC-A and MIC-B [58, 59]. HCMV-microRNAs have been reported.

9.2. Transmission and Protection

Transmission is achieved by contact with mucosal tissues or with infected secretions and excretions. HCMV is excreted in urine, saliva, breast milk, cervical secretions, and semen during primary and reactivated infections [60]. Ganciclovir, which inhibits the replication of all human herpes viruses, is usually used. Foscarnet is also approved in the USA. Acyclovir is not effective. Several pharmaceutical companies are working on the development of a vaccine [61].

10. Polyomavirus: SV40, JCV, BKV, and MCV

The participation of polyomaviruses in cancer processes remains controversial; however, the high tumorigenicity in cultured cells points to these as being true oncogenic agents [62-65]. Virus genomes require host machinery to replicate two proteins (T antigens) involved in the inactivation of tumor-suppressor genes, thus resulting in initiation of cell proliferation and oncogenic transformation.

10.1. Viral microRNAs

MCV encodes microRNA-M1; BK virus generates four (microRNA-B1-4); and SV40 and JC virus each produce two microRNAs (microRNA-J1 and microRNA-S1). These microRNAs, produced late during virus infection [66-68], play a role in degradation of viral early mRNAs. The SV40 microRNAs confer resistance in virus-infected cells to lysis by cytotoxic T cells [66].

10.2. Transmission and Protection

As the mechanism of human-to-human transmission of the polyomaviruses has not been firmly established, possible routes of human exposure are not known. There is not a vaccine available.

11. Murine Mammary Tumor Virus

The presence of murine mammary tumor virus (MMTV) in murine breast cancer tumors and its effect on carcinogenesis in humans by its counterpart (HMTV) has been one of the greatest controversies in retrovirology for the last fifteen years; causes mammary tumors in mice by insertional mutagenesis. The presence of viral antigens and nucleic acids (MMTV/HMTV) in human breast tumors has been reported [69].

11.1. Viral microRNAs

MMTV/HMTV-microRNAs have not been reported.

11.2. Transmission and Protection

Transmission in mice is from mother to pup via milk, and sequences have been detected in 5% of breast milk from healthy women [70].

12. Human Endogenous Retrovirus

The human genome contains a large number of human endogenous retroviruses (HERVs) sequences (8% of the human genome) that were derived from past retroviral infections and are permanently inserted into the genome; similar sequences are observed in all eukaryotic organisms. Many of these HERVs are transcribed and translated under normal physiological conditions, leading to the formation of complete viral particles [71].

12.1. Viral microRNAs

HERVs-microRNAs have not been reported.

12.2. Transmission and Protection

HERVs began as potential pathogenic agents in cancer and autoimmune processes [71].

13. Viral Vectors

The need for a vector (carrier) arises from the difficulties involved in the direct introduction of genetic material into a cell, because once inside the cell such genetic material is rapidly degraded by cellular mechanism(s) whose aims are to safeguard the integrity of the host genome. Viruses can be used as powerful tools for the introduction, into the target cell, of exogenous genetic material that can decrease the expression (silencing) of host gene(s) through RNA interference, thereby allowing analysis of the function of a gene or group of genes. Silencing can be achieved 1) by transition, utilizing interfering RNA directly, or 2) by long periods of time, used viral vectors (e.g., adenoviruses, retroviruses, lentiviruses, and herpesviruses) in order to introduce the RNA interference and integrate into the genome of the target cell and thence be transcribed and translated by the cellular machinery. The host immune response does not recognize these products as foreign and, therefore, does not remove them. Use of viruses as vectors requires the removal

of those viral genes concerned with the infectious and pathogenic capacity of the virus, leaving only those genes involved in the insertion of genetic material and the replacement for the host gene of interest [72].

13.1. Protection

Genesense® (also called augmerosen, bcl-2 antisense oligodeoxynucleotide G3139, and oblimersen sodium) is an antisense oligonucleotide, which target gene *Bcl2*, is used against melanoma and chronic lymphocytic leukemia. In 2010, the FDA did not approve Genesense® due to disappointing results in a melanoma trial [73].

14. Oncolytic Viruses

Tumor-selective replicating viruses offer appealing advantages over conventional cancer therapy and a promising a new approach for the treatment of human cancer. Virotherapy is not a new concept, but recent technical advances in the genetic modification of oncolytic viruses (vesicular stomatitis virus, reovirus, Newcastle disease virus, measles disease virus, H101, Onyx-15, oncoVEX, and JX594) have improved their tumor specificity, leading to the development of new weapons for the war against cancer [74].

15. Conclusions

Prevention is the best medicine; therefore, knowing the interaction between virus and host cell and the relationship of that interaction with cancer puts combating viral infection (e.g., the development of vaccines against oncoviruses) on the front lines of defense against cancer. When viral infection is established in the host, although the mechanism for triggering carcinogenesis is not strong, the viral infection affects several pathways, such as those of the cell cycle, apoptosis, senescence, DNA repair, or changes in metabolism, which increases not only the complexity of the disease, but also its prognosis, treatment alternatives, and preventive measures. The majority of current treatments for cancer has been developed by employing targeted cell proteins rather than viral elements. However, viral factors are equally important, and their use may open new lines of cancer treatment. Because virus involvement in cancer-related events is very broad, viruses can be used as molecular tools to assess genes that are over- or under- expressed in the homeostatic cell to treat direct or indirect causal agents of diseases.

One must bear in mind that the knowledge developed over the past 20 years concerning genomes, proteins (function and structure), and epigenetic factors [methylation, histone modifications, and ncRNAs (small and large)], when taken together, permit one to visualize and analyze complex entities (infections and cancer) as a whole. This knowledge promotes an understanding not only of the alterations caused at the molecular, cellular, and metabolic levels, but also of how to “correct” such alterations—a task that involves handling multiple events simultaneously. Cancer treatment ranges from prevention to control or cure and includes the sharing of results of scientific research (basic and applied) with all stakeholders (scientists, physicians, policy makers, and the general public).

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References

- [1] De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M: Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol.* 2012;13:607-615.
- [2] Breitbart M, Rohwer F: Here a virus, there a virus, everywhere the same virus? *Trends Microbiol.* 2005;13:278-284.
- [3] Koch, Robert. Die Aetiologie der Tuberkulose. *Journal of Molecular Medicine.* 1932;11:490-492.
- [4] Sarid R, Gao SJ: Viruses and human cancer: from detection to causality. *Cancer Letters.* 2011;305:218-227.
- [5] Roulston A, Marcellus RC, Branton PE: Viruses and apoptosis. *Ann Rev Microbiol.* 1999;53:577-628.
- [6] zur Hausen H: Papillomaviruses in the causation of human cancers—a brief historical account. *Virology.* 2009;384:260-265.
- [7] zur Hausen H: *Infections Causing Human Cancer.* Wiley-VCH; Chichester: John Wiley: Weinheim; 2006.
- [8] McLaughlin-Drubin ME, Munger K: Viruses associated with human cancer. *Biochim Biophys Acta.* 2008;1782:127-150.
- [9] Javier RT, Butel JS: The history of tumor virology. *Cancer Res.* 2008;68:7693-7706.
- [10] Cazalla D, Yario T, Steitz JA: Down-regulation of a host microRNA by a *Herpesvirus saimiri* noncoding RNA. *Science.* 2010;328:1563-1566.
- [11] Lewis BP, Burge CB, Bartel DP: Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell.* 2005;120:15-20.
- [12] Farh KK, Grimson A, Jan C, Lewis BP, Johnston WK, Lim LP, Burge CB, Bartel DP: The widespread impact of mammalian microRNAs on mRNA repression and evolution. *Science.* 2005;310:1817-1821.
- [13] Zheng J: Viral oncogenes, noncoding RNAs, and RNA splicing in human tumor virus. *J Biol Sci.* 2010;6:730-155.
- [14] Taylor GS, Blackburn DJ: Infectious agents in human cancers. *Cancer Lett.* 2011;305:263-78.

- [15] Gatto G, Rossi A, Rossi D, Kroening S, Bonatti S, Mallardo M: Epstein-Barr virus latent membrane protein 1 trans-activates miR-155 transcription through the NF-kappaB pathway. *Nucleic Acids Res.* 2008;36:6608-6619.
- [16] Amon W, Farrell PJ: Reactivation of Epstein-Barr virus from latency. *Rev Med Virol.* 2005;15:149-156.
- [17] Dourmishev LA, Dourmishev AL, Palmeri D, Schwartz RA, Lukac DM: Molecular genetics of Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) epidemiology and pathogenesis. *Microbiol Mol Biol Rev.* 2003;67:175-212.
- [18] Areste C, Blackburn DJ: Modulation of the immune system by Kaposi's sarcoma-associated herpesvirus. *Trends Microbiol.* 2009;17:119-129.
- [19] Gottwein E, Corcoran DL, Mukherjee N, Skalsky RL, Hafner M, Nusbaum JD, Shamulailatpam P, Love CL, Dave SS, Tuschl T, Ohler U, Cullen BR: Viral microRNA targetome of KSHV-infected primary effusion lymphoma cell lines. *Cell Host Microbe.* 2011;10:515-526.
- [20] Marshall V, Han SJ, Barsov E, Quinones O, Ray A, Yarchoan R, Ott D, Renne R, and Whitby D: KSHV encoded miRNA single nucleotide polymorphisms identified in clinical samples can affect miRNA processing and level of expression. *Infectious Agents and Cance.* 2012;7:P40.
- [21] Qin Z, Jakymiw A, Findlay V, Parsons C: KSHV-encoded microRNAs: lessons for viral cancer pathogenesis and emerging concepts. *Int J Cell Biol.* 2012;2012:603961.
- [22] de França TR, de Araújo RA, Ribeiro CM, Leao JC: Salivary shedding of HHV-8 in people infected or not by human immunodeficiency virus 1. *J Oral Pathol Med.* 2011;40:97-102.
- [23] de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H: Classification of papillomaviruses. *Virology.* 2004;324:17-27.
- [24] Bernard HU, Burk RD, Chen Z, van Doorslaer K, Hausen Hz, de Villiers EM: Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology.* 2010;401:70-79.
- [25] Van Doorslaer K, Tan Q, Xirasagar S, Bandaru S, Gopalan V, Mohamound Y, Huyen Y and McBride A: The Pappilloma Episteme: a central resource for papillomavirus sequence data and analysis. *Nucleic Acid Res.* 2013, in press.
- [26] Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group: Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348:518-27.
- [27] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189:12-19.
- [28] Parkin DM, Bray F: Chapter 2: The burden of HPV-related cancers. *Vaccine.* 2006;24:S3/11-25.
- [29] Zheng ZM, Baker CC: Papillomavirus genome structure, expression, and post-transcriptional regulation. *Front Biosci.* 2006;11:2286-2302.
- [30] Cai X, Li G, Laimins LA, Cullen BR: Human papillomavirus genotype 31 does not express detectable microRNA levels during latent or productive virus replication. *J Virol.* 2006;80:10890-10893.
- [31] Greco D, Kivi N, Qian K, Leivonen SK, Auvinen P, Auvinen E: Human papillomavirus 16 E5 modulates the expression of host microRNAs. *PLoS One.* 2011;6:e21646.
- [32] Shi W, Carr MJ, Dunford L, Zhu C, Hall WW, Higgins DG. Identification of novel inter-genotypic recombinants of human hepatitis B viruses by large-scale phylogenetic analysis. *Virology.* 2012;427:51-59.
- [33] El-Serag HB: Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology.* 2012;142:1264-1273.e1.
- [34] Yokosuka O, Arai M: Molecular biology of hepatitis B virus: effect of nucleotide substitutions on the clinical features of chronic hepatitis B. *Med Mol Morphol.* 2006;39:113-120.
- [35] Li L, Guo Z, Wang J, Mao Y, Gao Q: Serum miR-18a: a potential marker for Hepatitis B virus-related hepatocellular carcinoma screening. *Dig Dis Sci.* 2012;57:2910-2916.
- [36] WHO (2001). Introduction of hepatitis B vaccine into childhood immunization services. World Health Organization (ed) Geneva: No. Who/V&B/01.31, i-48.
- [37] Branda M, Wands JR: Signal transduction cascades and hepatitis B and C related hepatocellular carcinoma. *Hepatology.* 2006;43:891-902.
- [38] Aravalli RN, Steer CJ, Cressman ENK: Molecular mechanisms of hepatocellular carcinoma. *Hepatology.* 2008;48:2047-2063.
- [39] Llovet JM, Bruix J: Molecular targets therapies in hepatocellular carcinoma. *Hepatology.* 2008;48:1312-1327.
- [40] Slim J, Afridi MS: Managing adverse effects of interferon-alfa and ribavirin in combination therapy for HCV. *Infect Dis Clin North Am.* 2012;26:917-929.
- [41] Medication guide. FDA. Reference ID: 3166793.
- [42] Medication guide. FDA. Reference ID: 3149182.
- [43] Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, Nagata K, Hinuma Y: Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. *Nature.* 1981;294:770-771.
- [44] Proietti FA, Carneiro-Proietti ABF, Catalan-Soares BC, Murphy EL: Global epidemiology of HTLV-I infection and associated diseases. *Oncogene.* 2005;24:6058-6068.
- [45] Matsuoka M, Jeang K-T: Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat Rev Cancer.* 2007;7:270-280.
- [46] Yasunaga, J, Matsuoka, M: Leukaemogenic mechanism of human T-cell leukaemia virus type I. *Rev Med Virol.* 2007;17:301-311.
- [47] Macaire H, Riquet A, Moncollin V, Biémont-Trescol MC, Duc Dodon M, Hermine O, Debaud AL, Mahieux R, Mesnard JM, Pierre M, Gazzolo L, Bonnefoy N, Valentin H: Tax protein-induced expression of antiapoptotic Bfl-1 protein contributes to survival of human T-cell leukemia virus type 1 (HTLV-1)-infected T-cells. *J Biol Chem.* 2012;287:21357-21370.
- [48] Matsuoka M, Green PL: The HBZ gene, a key player in HTLV-1 pathogenesis. *Retrovirology.* 2009;6:71.
- [49] Doi K, Wu X, Taniguchi Y, Yasunaga J, Satou Y, Okayama A, Nosaka K, Matsuoka M: Preferential selection of human T-cell leukemia virus type I provirus integration sites in leukemic versus carrier states. *Blood.* 2005;106:1048-1053.

- [50] Derse D, Crise B, Li Y, Princler G, Lum N, Stewart C, McGrath CF, Hughes SH, Munroe DJ, Wu X. Human T-cell leukemia virus type 1 integration target sites in the human genome: comparison with those of other retroviruses. *J Virol.* 2007;81:6731-6741.
- [51] Diamantopoulos PT, Michael M, Benopoulou O, Bazanis E, Tzeletas G, Meletis J, Vayopoulos G, Viniou NA: Antiretroviral activity of 5-azacytidine during treatment of a HTLV-1 positive myelodysplastic syndrome with autoimmune manifestations. *Virol J.* 2012;9:1.
- [52] Elgui de Oliveira D: DNA viruses in human cancer: an integrated overview on fundamental mechanisms of viral carcinogenesis. *Cancer Lett.* 2007;247:182-196.
- [53] Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM: Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet.* 2007;370:59-67.
- [54] Moens U: Silencing Viral MicroRNA as a Novel Antiviral Therapy?. *J Biomed Biotechnol.* 2009;419539.
- [55] U.S. Department of Health and Human Services' *Guidelines for the Use of Reviewed Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (available at <http://aidsinfo.nih.gov/guidelines>).
- [56] Michaelis M, Doerr HW, Cinatl J: The story of human cytomegalovirus and cancer: increasing evidence and open questions. *Neoplasia.* 2009;11:1-9.
- [57] Zhang G, Raghavan B, Kotur M, Cheatham J, Sedmak D, Cook C, Waldman J, Trgovcich J: Antisense transcription in the human cytomegalovirus transcriptome. *J Virol.* 2007;81:11267-11281.
- [58] Bennett NJ, Ashiru O, Morgan FJ, Pang Y, Okecha G, Eagle RA, Trowsdale J, Sissons JG, Wills MR: Intracellular sequestration of the NKG2D ligand ULBP3 by human cytomegalovirus. *J Immunol.* 2010;185:1093-102.
- [59] Wilkinson GW, Tomasec P, Stanton RJ, Armstrong M, Prod'homme V, Aicheler R, McSharry BP, Rickards CR, Cochrane D, Llewellyn-Lacey S, Wang EC, Griffin CA, Davison AJ: Modulation of natural killer cells by human cytomegalovirus. *J Clin Virol.* 2008;41:206-212.
- [60] Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH: Cytomegalovirus infection. *Pediatr Rev.* 2012;33:156-163.
- [61] Beam E, Razonable RR: Cytomegalovirus in Solid Organ Transplantation: Epidemiology, Prevention, and Treatment. *Curr Infect Dis Rep.* 2012;14:633-41.
- [62] Goel A, Li MS, Nagasaka T, Shin SK, Fuerst F, Ricciardiello L, Wasserman L, Boland CR: Association of JC virus T-antigen expression with the methylator phenotype in sporadic colorectal cancers. *Gastroenterology.* 2006;130:1950-1961.
- [63] McCabe MT, Low JA, Imperiale MJ, Day ML: Human polyomavirus BKV transcriptionally activates DNA methyltransferase 1 through the pRb/E2F pathway. *Oncogene.* 2006;25:2727-2735.
- [64] Feng H, Shuda M, Chang Y, Moore PS: Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 2008;319:1096-1100.
- [65] Jiang M, Abend JR, Johnson SF, Imperiale MJ: The role of polyomaviruses in human disease. *Virology.* 2009;384:266-273.
- [66] Sullivan CS, Grundhoff AT, Tevethia S, Pipas JM, Ganem D: SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. *Nature.* 2005;435:682-686.
- [67] Seo GJ, Fink LH, O'Hara B, Atwood WJ, Sullivan CS: Evolutionarily conserved function of a viral microRNA. *J Virol.* 2008;82:9823-9828.
- [68] Seo GJ, Chen CJ, Sullivan CS: Merkel cell polyomavirus encodes a microRNA with the ability to autoregulate viral gene expression. *Virology.* 2009;383:183-187.
- [69] Etkind P, Du J, Khan A, Pillitteri J, Wiernik PH: Mouse mammary tumor virus-like ENV gene sequences in human breast tumors and lymphoma of breast cancer patient. *Clin Cancer Res.* 2000;6:1273-1278.
- [70] Johal H, Ford C, Glenn W, Heads J, Lawson J, Rawlinson W: Mouse mammary tumor like virus sequences in breast milk from healthy lactating women. *Breast Cancer Res Treat.* 2011;129:149-155.
- [71] Voisset C, Weiss RA, Griffiths DJ: Human RNA "tumor" viruses: the search for novel human retroviruses in chronic disease. *Microbiol Mol Biol Rev.* 2008;72:157-196.
- [72] Gentner B, Naldini L: Exploiting microRNA regulation for genetic engineering. *Tissue Antigens.* 2012;80:393-403.
- [73] Abou-Nassar K, Brown JR: Novel agents for the treatment of chronic lymphocytic leukemia. *Clin Adv Hematol Oncol.* 2010;8:886-895.
- [74] Zeyaullah M, Patro M, Ahmad I, Ibraheem K, Sultan P, Nehal M, Ali A. Oncolytic viruses in the treatment of cancer: a review of current strategies. *Pathol Oncol Res.* 2012;18:771-81.
- [75] Vergoulis T, Vlachos I, Alexiou P, Georgakilas G, Maragkakis M, Reczko M, Gerangelos S, Koziris N, Dalamagas T, Hatzigeorgiou AG; Tarbase 6.0: Capturing the Exponential Growth of miRNA Targets with Experimental Support NAR (Database issue 2012).