The viruses in the human oncogenesis

Anggi Vélez-Bohórquez¹, Mabel Bohórquez-Lozano²,*, Magdalena Echeverry-de-Polanco³

Abstract
Based on epidemiological associations and experimentation, relationships between viruses and cancer have been established. For more than 14 million new cases of cancer per year, it is estimated that 15% are related to viral agents. Epithelial, hematolymphoid and mesenchymal malignancies related to different viruses have been documented such as Epstein Barr, Kaposi’s sarcoma, hepatitis B and C, human lymphotropic type 1, Merkel’s carcinoma and human papilloma. New virus with oncogenic potential such as cytomegalovirus, JC polyoma virus and BK have been described. The interaction of the viruses with the host induces oncogene activation, inhibition of tumor suppressor genes and activation of miRNAs, as determining factors in the development of cancer. The pathology is initiated with the infection that induces the deregulation of cell signaling. The Epstein Barr virus is the oncogenic prototype, with 1% of the human cancers related to it.

Keywords: Neoplasms, virology, pathogenesis

Introduction
Since the early twentieth century, it was suspected that cell transformation could involve external agents called “filterable agents free of cells”, capable of reproducing neoplastic manifestations in experimental animals¹,². Later on, these “agents” were classified as viruses, giving rise to the concept of oncogenic viruses in 1970¹. Viruses are etiological agents of a vast number of human pathologies, from acute self-limiting infections to potentially fatal conditions, among of them cancer which is consider a worldwide public health problem. The rate of incidence of cancer includes 14.1 million new cases and 8.2 million deaths per year, of those, 57% (8 million) of the new cases and 65% (5.3 million) of cancer deaths occur in developing countries¹.

The different types of cancer of viral origin are multifactorial and, like non-infectious ones, seem to be a biological anomaly since the tumors do not increase the transmissibility of the virus, nor do they offer any specific advantage. In short, cancer seems to be the final event of the infection. Due to this, most people exposed to these viruses do not develop malignancy, confirming the need for other factors to trigger oncogenesis⁴. The cause of these malignancies is based on postulates as old as the one attributed to Galileo Galilei: “An agent causes disease when it is necessary and sufficient for the disease to occur”. This postulate has evolved through scientist such as Henle, Koch and Hill, that established the criteria needed to declare microorganisms as the causal agents of disease. These criteria include the biological characteristics of the

1 Programa de Medicina Universidad del Tolima, Ibagué, Colombia
2 Institución: Universidad del Tolima departamento: Grupo de Citogenética, filogenia y evolución de poblaciones, Ibagué, Colombia
3 Institución: Universidad del Tolima departamento: Grupo de Citogenética, filogenia y evolución de poblaciones, Ibagué, Colombia
* Autor para correspondencia.
Correo electrónico: mebohorquez@ut.edu.co
Grupo de Citogenética, filogenia y evolución de poblaciones, bloque 17
Universidad del Tolima. Código postal: Nro 730006299
Barrio: Santa Helena parte alta, Ibagué Tolima Colombia. Tel.: 3118488284

Recibido: 05/03/2018; Aceptado: 26/04/2018
microorganism, its effects on the host, the reproducibility of these by different researchers and the epidemiological relationships. Thanks to these scientific methods, the infectious agents that cause cancer have been divided into two categories: direct carcinogens, which express oncoproteins that contribute to the transformation and indirect carcinogens that through the necessary process of infection and inflammation, eventually cause carcinogenic mutations.

It is estimated that 15% of cancer cases are related to viral agents, which is why, in this review of literature, readers are offered an update on the subject, which considers the different oncogenic viruses, their pathogenic mechanisms and the interaction with the host cell, which culminates in tumorigenesis.

**Materials and methods**

**Search Strategies**
The PRISMA statement (http://www.prisma-statement.org/) was incorporated, a systematic search was made in the electronic databases: NCBI (PuMed), MEDLINE (OvidSP), Scopus (ScienceDirect), combining the terms Search (MesH): “Neoplasm”, “Virology”, “Related” and “Etiopathogenic”, the DOI of the articles was verified at http://www.doi.org/.

**Inclusion and exclusion criteria**
We included articles that offered a review of the topic in humans in the last 5 years, with the indicated search strategy; The selection of articles is detailed in figure 1.

Types of studies excluded: (I) Clinical trials of drugs and vaccines; (II) Comparison of treatments or diets in patients; case reports; (IV) Syndromes (V) comments and editorials. Data on geographical location, study population, study design and results were extracted, according to the acronym PICO, see table 1.

The full text documents were independently evaluated by two reviewers, the disagreements were resolved by consensus, with the participation of a third party when it was necessary (Figure 1).

**Evaluation of quality**
The evaluation of the systematic reviews included in the comparative analysis was done through the: “Critical Appraisal Skills Program” (CASP), http://www.casp-uk.net/#casp-tools-checklists/c18f8; a minimum inclusion score of 6/10 was established, determined by two authors and based on the analysis of the text of the published version.

The methodological quality of the 45.95% of the studies is between 8 and 10 points. The average score is 7.37. No publication showed a methodological quality of less than six.

**Results**
A total of 34 articles were selected for the comparative analysis, of which 33 (97%), relate the cancer with molecular details of viruses considered oncogenic. The majority of these (29.4%) correspond to journals in the United Kingdom, with

---

**Figure 1.**

Identification

PubMed – NCBI
530

SciELO – LILACS
38

2 MeSH terms
Virology, Neoplasm

Screening

Excluded for being:
• Clinical trial
• Case report
• Language

288

268

175

37

Included

34

Included or revised

Revision of titles

Revision of abstract

Full Reading, excluding for not fulfill all the criteria.
The viruses in the human oncogenesis

Table 1. Inclusion criteria according to acronym PICO *.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Results according to PICO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Studies of systematic reviews that include pathogenic aspects in which the interaction of the viruses with the host is circumscribed as a determining factor in the development of human malignancies.</td>
</tr>
<tr>
<td>Population</td>
<td>Malignant neoplasm associated to oncogenic viruses</td>
</tr>
<tr>
<td>Intervention</td>
<td>None</td>
</tr>
<tr>
<td>Outcome</td>
<td>Classification of oncogenic viral particles and their cellular targets related to the infection and its oncogenic effects</td>
</tr>
</tbody>
</table>

*The PICO process (acronyms defining (P) population, (I) intervention, (C) comparison and (O) outcome).

an average H index (IHP) of 133, followed by publications from the United States and China. Of the 34 articles, 10 of them present a review about the Epstein Barr virus (29.4%); 8 of Kaposi’s sarcoma virus (23.5%); 6 of human papilloma virus (17.6%); 5 of hepatitis C (14.7%); 4 of hepatitis B (11.7%); 3 of HTLV-1 (8.8%); 2 of Merkel virus (5.8%) and 1 of Cytomegalovirus (2.9%).

Viruses have been identified as etiological agents of cancer since 1909 when Peyton Rous started his research on the transmissibility of sarcoma in hens5, followed by the description of oncogenic viruses in mammals in the thirties, with accelerated development in tumor virology in the subsequent decades7. The twentieth century culminated with Harold zur Hausen’s declaration of the human papillomavirus as a high-oncogenic risk and describing it as a “stage setter” for cervical cancer based in long term research6; this announcement was recognized with the Nobel Prize in 20088. With the advances in genomics and the description of the pathogenicity of the different viral families, viral molecules closely related to the development of cancer have been identified4. The families of viruses related to cancer in the different publications are: Herpesviridae - double-strand linear DNA, Hepadnaviridae - double-circular DNA chain, Flaviviridae - single-chain RNA, Retroviridae - single-chain RNA, Polymaviridae - double-stranded circular DNA, Papilomaviridae - Double linear DNA4. These families have viruses of different genomic and transmissibility characteristics (sexual, oral fecal, fomites, aerial droplets and even blood products transfusions); cellular tropism (immune system, mucous membranes or parenchymal tissues). In addition, they can have diverse pathogenic mechanisms (Table 2) including: infection, inflammation - TNF, IL6, IL8 -, viral persistence and oncogenic mechanisms (Table 3) such as transformation, key in the multiple steps necessary for viral oncogenesis10,11. Recently, Lin-Tao, et. al., postulated that after the transformation, there is an uncontrolled proliferation and metabolic reprogramming that facilitate the production of energy and molecular synthesis12. In the last four decades, the international agency for cancer research IARC reports to all these families as human carcinogens with different degrees of risk, the highest degree is # 1 in which there is enough evidence linking a certain virus with a malignancy, such as the Epstein Barr virus with lymphomas and epithelial tumors, as detailed in Table 313,14.

Virus related to tumors of hemolymphoid origin

**Epstein Barr**: This virus infects B cells and is expressed in different ways, depending on the oncological pathology it generates: 1. Type I latency (15), characterized by the nuclear antigen EBNA-1. It promotes cell proliferation by activating the c-MYC complex and it prevents the presentation of antigens avoiding the protooncogenic degradation characteristic of Burkitt’s lymphoma (16); 2. Type II latency, EBNA in conjunction with membrane proteins LMP-1 and 215; characteristic of Hodgkin’s lymphoma, in which LMP-1 deregulates the apoptotic pathways by activating p13K and the B cell receptor (BCR), which, in turn, promotes genetic damage by translocation and negative regulation of tumor suppressors through miR21; the immortalization of these cells is attributed to EBNA-3C by interaction with cell cycle control points and apoptotic block17,18; 3. Type III latency associated with post-transplant lymphoproliferative disorders is associated with elevation of cellular miR155 that activates BCR, promoting proliferation15,19.

**Hepatitis C (HCV)**: This virus establishes its oncogenic action in marginal zone lymphoma and others with greater malignancy such as diffuse large B-cell lymphoma by means of the structural protein E2, which, by binding to CD81, activates proliferation upon stimulation CD19, CD21 and BCR20. Through NS3 and E7, pro-inflammatory interleukins are activated that increase somatic hypermutation and genetic translocation21, with the consequent overexpression of BLC-2 and the reduction of caspase action, causing apoptotic dysfunction. MirR122 is a miRNA specific to the liver18,22, whose mechanism of action is still uncertain. It was described by Lin and Flemington19 as a positive regulator of virus replication, which causes an increase in the number of copies.

**Herpes type 8**: It is associated with lymphomas in the serous cavities (PEL). The production of IL-6 induces the production of its human analog, resulting in cell proliferation. In addition, this viral cyclin gene (vCyc), is integrated into the genome of the B lymphocytes, generating the right environment for cell expansion and facilitating transformation23.

**Human lymphotrophic type 1 (HTLV1)**: HTLV1 is the causal agent of adult T cell leukemia. It infects dendritic cells and T lymphocytes, where the viral protein Tax recruits transcription factors, resulting in accelerated mitosis. The multiple integration of multiple viral copies in the host genome promotes the structural damage of DNA24. The HBZ protein activates the alternative pathway NF-kB, promoting proliferation and activation of the transcription of E2F1 that increases the viral load and the action of telomerases25.
Viruses Related to Tumors of Epithelial Origin
Nasopharyngeal and Oropharyngeal carcinoma: It is a distinct histological subtype of head and neck tumors, with variants such as keratinized and non-keratinizing carcinoma. This in turn, has a subtype with abundant lymphoid infiltrate, associated with virus infection. EBV infects epithelial cells by transforming beta 1 growth factor, to then activate type II latency and express EBNA1 and LMP1 and LMP2A. This causes dysregulation of proliferation through MAP-kinase, c-MYC and suppression of p13K and p16. EBV expresses BARTs, a family of multi-spliced transcriptional products of the viral genome, with high expression in infected epithelial cells. Its main function seems to be to attack non-coding cellular RNAs responsible for regulating genetic expression. BARTs produce multiple microRNAs that have apoptotic and anti-proliferative mechanisms.

Gastric carcinoma: It has been associated with bacterial infection by Helicobacter pylori, as well as with infection by EBV. Positive tumors for this virus occur in two histological types: conventional adenocarcinomas (16%) and gastric carcinomas with lymphoid and epithelial phenotype (89%). Tumors positive for EBV are characterized by infecting almost all tumor cells; they are detected by the presence of antigens EBE1 and 2, small non-coding RNAs, with oncogenic properties, such as efficient proliferation of transformed B cells and Activation of insulin-1-like growth factor as an autocrine factor for proliferation. The infection is established in its type I or II latency form, with expression of EBNA1, BARTs, and LMP2A, which play an essential role in epigenetic abnormalities by promoting the methylation of PTEN (enzyme-suppressor tumor).

Table 2. Viral families, oncogenic viruses, genomics characteristics, transmissibility and pathogenesis.

<table>
<thead>
<tr>
<th>Genre</th>
<th>Genome</th>
<th>Virus</th>
<th>IARC Group</th>
<th>Replication</th>
<th>Transmission</th>
<th>Cellular tropism</th>
<th>Primary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocrypto-virus</td>
<td>Linear double-stranded DNA</td>
<td>EBV HHV4</td>
<td>1</td>
<td>Lytic and latency. The core. They produce: immediate mRNAs, they encode proteins that initiate and regulate viral transcription, early mRNAs encode nonstructural proteins involved in DNA replication, and late mRNAs encode structural capsid protein and envelope glycoproteins.</td>
<td>Saliva</td>
<td>B lymphocytes and epithelial cells.</td>
<td>Asymptomatic. Mononucleosis.</td>
</tr>
<tr>
<td>Rhadino-virus</td>
<td>Circular double-stranded DNA</td>
<td>KSHV HHV8</td>
<td>1</td>
<td>In the core. It uses the viral DNA polymerase to generate a complete circular chain and the cellular RNA polymerase for the transcription of the initial products (HBCAg, HBeAg and DNA polymerase of the virus and the pregenic RNA) and then a reverse transcriptase that encodes the viral DNA.</td>
<td>Sexual contact</td>
<td>B lymphocytes periphery mononuclear cells.</td>
<td>Asymptomatic.</td>
</tr>
<tr>
<td>Orto-hepadna-virus</td>
<td>Circular double-stranded DNA</td>
<td>HBV</td>
<td>1</td>
<td>In the cytoplasm. Income, denudation followed by translation into a polyprotein that is then fragmented, including a polymerase that directs the transcription and replication, for postereiation in the form of vesicles.</td>
<td>Sexual, parenteral</td>
<td>Hepatocytes</td>
<td>Acute hepatitis and chronic 10%.</td>
</tr>
<tr>
<td>Hepaci-virus</td>
<td>Single chain RNA</td>
<td>HCV</td>
<td>1</td>
<td>Through the reverse transcriptase copies the RNA into double-stranded DNA, which is integrated into the chromosome of the host and replicated with the cell as a provirus by the RNA polymerase of the host, thus producing genomic RNA and Spliced mRNAs, encode envelope glycoproteins and regulatory proteins.</td>
<td>Fluids with cells</td>
<td>T lymphocytes</td>
<td>Asymptomatic.</td>
</tr>
<tr>
<td>Deltaretro-virus</td>
<td>RNA</td>
<td>HTLV1</td>
<td>1</td>
<td>In the nucleus, the transcription is carried out by the RNA polymerase of the host and leads to the synthesis of viral proteins, for their samplings and release when the cell dies.</td>
<td>Not clear. Maybe respiratory droplets.</td>
<td>Epithelial cells of hair follicles. Merkel’s cells</td>
<td>Asymptomatic.</td>
</tr>
<tr>
<td>Polyoma-virus</td>
<td>Circular double-stranded DNA</td>
<td>MC</td>
<td>2A</td>
<td>In the core. The RNA polymerase of the host transcribes the early genes, with subsequent synthesis of the early proteins, the DNA synthesis directed by the DNA polymerase of the host cell. The DNA of the virus can be integrated into the chromosomes of the host.</td>
<td>Sexual, mucosal contact.</td>
<td>Stratified epithelial cells</td>
<td>Warts, condyloma acuminatum, oral and laryngeal papillomatosis</td>
</tr>
<tr>
<td>Papova-virus</td>
<td>Double-stranded DNA</td>
<td>VPH</td>
<td>1</td>
<td>In the core. The RNA polymerase of the host transcribes the early genes, with subsequent synthesis of the early proteins, the DNA synthesis directed by the DNA polymerase of the host cell. The DNA of the virus can be integrated into the chromosomes of the host.</td>
<td>Sexual, mucosal contact.</td>
<td>Stratified epithelial cells</td>
<td>Warts, condyloma acuminatum, oral and laryngeal papillomatosis</td>
</tr>
</tbody>
</table>

Table 3. Oncogenic virus, viral mechanism, cellular target.

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Virus</th>
<th>Oncogenic viral particle</th>
<th>Cellular target/ Cellular effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell Lymphoma</td>
<td>Epstein Barr</td>
<td>EBNA 1</td>
<td>Protooncogene translocation c-MYC (8-14), proliferation.</td>
<td>15, 16, 19, 30</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td></td>
<td>EBNA 3C</td>
<td>Cell immortalization</td>
<td>17</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td></td>
<td>LMP1</td>
<td>Deregulation of proliferation: MAP-Kinasa</td>
<td>17</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Epstein Barr</td>
<td>EBNA 3C</td>
<td>Cell immortalization</td>
<td>17</td>
</tr>
<tr>
<td>T/NK-cell lymphoma</td>
<td></td>
<td>LMP1</td>
<td>Deregulation of proliferation: MAP-Kinasa</td>
<td>17</td>
</tr>
<tr>
<td>Leukemia/ Adult T-cell lymphoma</td>
<td></td>
<td>miR155, miR146: induces uncontrolled proliferation</td>
<td>miR21: down-regulation of tumor suppressors</td>
<td>16, 18, 19, 29</td>
</tr>
<tr>
<td>B-cell Lymphoma</td>
<td>Epstein Barr</td>
<td>E2</td>
<td>Bind to CD81 that activates CD19-CD21 and proliferation</td>
<td>19, 20</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>Hepatitis C</td>
<td>NS3 y E7</td>
<td>Translocation 14-18 overexpression of BCL-2</td>
<td>20, 21, 65</td>
</tr>
<tr>
<td>MALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hodgkin lymphoma</td>
<td>Herpes B</td>
<td>vCyc</td>
<td>Integrates the host genome and generates cell expansion</td>
<td>17, 23</td>
</tr>
<tr>
<td>Leukemia/T-cell lymphoma</td>
<td>HTLV-1</td>
<td>Tax</td>
<td>Recruit transcription factors, activate the NF-kB and AKT pathways; it results in proliferation. Accelerates the cell cycle, causes structural DNA damage, inhibits repair and facilitates overduplication of centrosomes</td>
<td>17, 24, 65</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
<td>HBZ</td>
<td>Activates the alternative NF-kB pathway, which determines cell proliferation; Promotes the transcription of factor E2F1 and proliferation, increases the viral load and the action of telomerases.</td>
<td>24</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>Epstein Barr</td>
<td>EBNA 1</td>
<td>Protooncogene translocation c-MYC (8-14), proliferation.</td>
<td>15, 30</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td></td>
<td>LMP1</td>
<td>DNA methylation and suppression of p16</td>
<td>15, 27</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td></td>
<td>Pre-S2 deletion mutant proteins</td>
<td>TGF-β, IL1-β y TNF-α active JNK that increases the rate of cell proliferation</td>
<td>31, 34</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
<td>STAT3 y NF-kB</td>
<td>Antiapoptotic and regulate tumor angiogenesis</td>
<td>32</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
<td>Viral protein HBx</td>
<td>Activates mitogenic signals, generates chromosomal instability, increased metalloproteinase matrix production, which facilitates cell migration</td>
<td>4, 32, 33</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
<td>Viral protein HBVs</td>
<td>Mitochondria: inhibits JTB by increasing the life of the cell and preventing apoptosis</td>
<td>41</td>
</tr>
<tr>
<td>Merkel carcinoma</td>
<td>Merkel</td>
<td>T (large) antigen</td>
<td>Bind PRB, active proliferation</td>
<td>5, 38</td>
</tr>
<tr>
<td>Cervical</td>
<td>Merkel</td>
<td>T (small) antigen</td>
<td>It binds and reprograms PP2A, promotes cell cycle and transformation.</td>
<td></td>
</tr>
<tr>
<td>Skin: Baso- and Squamous-cell carcinoma</td>
<td>HPV</td>
<td>E6</td>
<td>Degrade p53, with deregulation</td>
<td>39, 41, 43</td>
</tr>
<tr>
<td>Oropharyngeal Carcinoma</td>
<td></td>
<td>E7</td>
<td>Degrade PRB</td>
<td>39, 43</td>
</tr>
<tr>
<td>Squamous neoplasm of the ocular surface</td>
<td></td>
<td>miR100: inhibits PLK1 gene, promotes early carcinogenesis</td>
<td></td>
<td>19, 43</td>
</tr>
</tbody>
</table>
**Lymphoepithelial carcinoma:** Es un carcinoma poco diferenciado con infiltrado linfocítico denso\(^{26}\). Ha sido descrito en ubicaciones como estómago, esófago, tonsilas, glándulas salivales, timo, pulmones y biliárias. \(^{10}\) La pobre diferenciación de estos epitelios y un entorno inflamatorio molecular son los mecanismos oncopigénicos característicos del virus Epstein Barr, caracterizado por llaga II que interrumpe múltiples procesos celulares y señales de las vías de señalización mencionadas anteriormente.

**Hepatocarcinoma (HCC):** Este carcinoma tiene un desarrollo asociado con la fibrosis. Epidemiológicamente, se ha descrito en alrededor de 80% de los casos con la infección crónica por el virus de la hepatitis B (HBV) y el virus de la hepatitis C (HCV), pasando por la infección inicial hasta uno de los factores más importantes de riesgo. En el proceso de infección viral, la cirrosis no se alcanza hasta 20 años después de la infección y el oncogénesis toma al menos 10 años más. \(^{31}\) Estas infecciones se distribuyen ampliamente en el mundo y tienen una variedad de mecanismos oncopigénicos \(^{32}\) como sigue:

a. El medio microinflamatorio que promueve la activación de la transformación del factor de crecimiento en beta transformada (TGF-β) estimula mecanismos oncopigénicos tales como JNK (miembro de la familia MAPK), produciendo rápida división celular con pérdida de reparación genética. Otros productos inmunológicos como IL-1β, TNF-α y IL-6 (que generan resistencia a apoptosis), son capaces de activar estos mecanismos. TGF-β mantiene una relación con pSmad3C en condiciones normales, pero cuando este se manifiesta, se activa STAT3 y inhibe la apoptosis de células transformadas, un paso crítico para el desarrollo de malignidad.\(^{31}\)

b. La inducción de daño oxidativo en lipidos, proteínas mitogénicas como MAPL, P13K, p53 y β-catenina, y en DNA. Estas especies reactivas de oxígeno inducen señales de calciun intracelular, aumentando sus concentraciones mediante resistencias mitocondriales, activando STAT3 y inhibiendo apoptosis.\(^{32}\)

c. La inserción de DNA viral en el genoma del huésped en etapas tempranas de infección, lo que en algunos casos resulta en modificaciones genéticas, como instabilidad genómica, amplificaciones y translocaciones cromosómicas.\(^{32,33}\) Varios estudios han descubierto que integraciones comunes, amplificaciones y translocaciones cromosómicas son los principales eventos genéticos, tales como instabilidad genómica, desarrollo tumoral y poliploidía, inhibiendo JTB por incremento de la motilidad celular, facilitando metástasis.\(^{32}\) PreS2 también interactúa con c-Jun y fosfoprotéinas pRB.\(^{34}\)

d. Los productos del virus como Hbx y PreS / S. Hbx es un proteínoma viral que activa mentioned mitogenetic factors. It also binds directly to p53 inhibiting apoptosis; it has been identified as a paracrine activator of stellate cell activation, promotes cellular migration by increasing intracellular meta-proteína y angioígenos when activating HIF1 that activates VEGF y ANG2. PreS / S is a viral antigen retained in the endoplasmic reticulum of the hepatocyte that generates oxidative stress, this retention activates cyclin A and therefore proliferation, as well as the over-duplication of centrosomes. It also activates hTERT that increases the activity of telomerase, generating telomere instability and even polyploid y inhibits JTB by increasing cell motility, facilitating metastasis. PreS2 also interacts with c-Jun and hyperphosphorylates pRB.

e. El aberrante metilación de áreas promotoras (CpG islas), que inactivan supresores tumorales en etapas tempranas de la enfermedad. El enzima DNMT está en el proceso de mantenimiento de metilación del gen de la célula, con una regulación de este enzima por Hbx. Tiene un preferencia por metilación de segmentos que controlan progresión, sobre todo las translocaciones cromosómicas, y participa en la inducción de la muerte celular, facilitando la metástasis.\(^{32}\) PreS2 también interactúa con c-Jun y fosfoprotéinas pRB.

**The control of the microRNAs:** Multiple interaction between the virus and these non-coding particles have been established. The following are highlighted: miR602 attacks RASSF1A; miR143 usually considered a tumor suppressor, which contributes to metastasis by over expression, inhibiting the expression of FNDC3b of the fibronectin 3 gene, whose product regulates cell motility. HBV and HCV share multiple mechanisms of transformation and tumorigenesis, with small differ-
The viruses in the human oncogenesis

The role of HPV in keratinocytic carcinomas such as basal cell carcinoma and squamous cell carcinoma of the skin is not fully understood. Multiple clinical, epidemiological and experimental studies suggest a carcinogenic role of type B HPV in the development of these malignancies. This includes the viral characteristics (presence of E6 and E7 that degrade tumor suppressors and activate telomerase) and other factors such as exposure to UV radiation and the response of immunocompromised patients. That is, a patient with a deficient immune system has more viral copies that cause damage to the DNA and prevent its repair, blocking in turn apoptotic pathways, these added factors culminate in the development of cancer.

**Tumors of Mesenchymal Origin**

Herpes virus 8 or Kaposi’s sarcoma virus induces transformation of mesenchymal cells, through different routes. LANA-1 binds to tumor suppressor p53 and inhibits the ability to induce apoptosis, as well as the pRB controller to modulate the cell cycle transition from G1 to S, where it allows replication and viral latency. Prox-1 and vFLIP induce the lymphoendothelial and endothelial-mesenchymal transition resulting in the fusiform morphology of the cells. Kaposins A, B and C, and the K1 ORF are tumor promoters. Lin and Flemington, describe the viral microRNA K12-1, which allows the increase of the cell cycle speed when arresting p53, K12-3 and K12-7. This selectively activate the secretion of IL6 and IL10 promoting cell growth, the angiogenesis and the suppression of T cells.

In this review, seven viruses are reported as causal agents of cancer in humans, but the literature proposes some others that have viral characteristics compatible with the oncogenic mechanisms described above, along with epidemiological and experimental associations that sustain them. Among them, the Cytomegalovirus of the herpesviridae family are found as potential causal agents of CNS malignancies (gliomas and multiform glioblastoma), colon and prostate carcinoma.JC and BK viruses of the polyomaviridae family are causal agents of tumors of the central nervous system and colorectal carcinoma. The postulated mechanisms for tumorigenesis are explained in Table 4. There has been descri-
Table 4. Viruses and possible oncogenic mechanism, without enough evidence.

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Virus</th>
<th>Oncogenic viral particle</th>
<th>Cellular target/ Cellular effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioma</td>
<td>Cytomegalovirus</td>
<td>Prolonged infection of monocytes and macrophages.</td>
<td>TAMs, releasers of IL6, IL10 TGF-β, that activate proliferation by means of STAST 3</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Gen US3</td>
<td>Retention of MHC I in the endoplasm reticulum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>US28</td>
<td>Promotes cellular migration by RANTES and MCOP-1</td>
<td></td>
<td>51, 54</td>
</tr>
<tr>
<td>Colon Carcinoma</td>
<td>UL 3</td>
<td>It binds to caspase-8 and inhibits Fas-mediated apoptosis.</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>UL37</td>
<td>Inhibits proapoptotic pathways, Bax and Bak.</td>
<td></td>
<td>51, 54</td>
</tr>
<tr>
<td></td>
<td>Gen UL83</td>
<td>Produces pp65 that blocks the presentation of antigens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Carcinoma</td>
<td>Cytomegalovirus</td>
<td>Mutagenics, break into DNA repair interfering with RM and ATR.</td>
<td>Delete p53 and pRb</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>IE1</td>
<td>Mutagenics, break into DNA repair interfering with RM and ATR.</td>
<td>Delete p53 and pRb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IE2</td>
<td>Disable p53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mirR-UL112</td>
<td>Suppress the expression of MHC I</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RNABeta 2.7</td>
<td>Mitochondria, prevents apoptosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UL36</td>
<td>Inhibits Fas-mediated apoptosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UL123/124</td>
<td>Inhibits apoptosis by activating PI3 kinase.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Stimulates hTERT increases the activity of telomerase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Induces CD40 expression by increasing proliferation cell signaling</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>Polyomavirus (JC y BK)</td>
<td>TAG</td>
<td>Inhibits Rb, releasing E2F. Inhibits p53</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>tAG</td>
<td>Deregulates WTN of β-catenin and stimulates gene expression.</td>
<td>Activates PP2A, affects the cytoskeleton and promotes migration.</td>
<td></td>
</tr>
</tbody>
</table>

be another virus linked to the development of breast cancer like bovine leukemia virus (BLV), mouse mammary tumor-like virus (MMTV) both retroviruses55 their oncogenic mechanism still no clear, there is substantial information, but cannot be regarded as conclusive56 more over in recent studies has been demonstrated the interaction of different types of virus, Drop et. al.57 describes confection between 22-34%, involucre tow or more of the following viruses: BKV, HPV, CMV, HSV and EBV, this combinations can induce transformation or ether exhibit a more rapid developing; so that associated with esophagus, prostate, bladder, breast, lung, colon and even central nervous system58, not even this association are no documented properly.

**Discusión**

Pathologies of viral origin begin at the time of infection, although this is only one of the steps for the development of malignancy. The process of cellular transformation begins with the deregulation of cell signaling induced by the virus, stimulating oncoproteins that tend to have self-sufficiency in replication and adaptation, insensitivity to inhibitory and apoptotic signals, as well as to angiogenesis, tissue invasion and metastasis59,60. These provide proliferative advantages even under conditions of nutrients and poor oxygen61.

The Epstein Barr virus is the oncogenic prototype, one of the most ubiquitous and successful known viruses. It has developed strategies to infect multiple cell types, evade the immune system, develop viral latency and contribute to the development of malignancies in the three types of tissue mentioned in this review (lymphoid, epithelial and mesenchymal), to the point that 1% of human cancer types are related to these agents7,30,62.

Viral infections are one of the risk factors for the development of cancer. Research and understanding of the pathogenic mechanisms will allow the development of strategies for the prevention of these malignancies. The development of effective vaccination strategies, as reported by Stanley in a recent review about hepatitis B virus infection, indicating that there are approximately 250 million people infected and about 887,000 deaths in 2015. In addition, it appears that up to 50% of children infected at an early age develop cirrhosis or carcinoma hepatocellular. The implementation of the universal vaccination program in 1992, resulted in a decrease in the rate of carriers of the virus. Regarding the human papillomavirus, approximately 290 million women are estimated to be infected. In an optimal scenario, in countries with more than 50% vaccine coverage, the v2VPH v4 HPV vaccine could reduce the incidence of cervical cancer by 70%, and the v9VPH could reduce it by 90%. The infections by HPV16 and 18 were decreased by 68%, with a reduction of cross infection by strains 31, 45 and 3363. In the near future, specific treatments should be implemented, perhaps through vectors of genetic therapies or by the use of oncolytic therapy agents64,65.
Acknowledgments

To University of Tolima for the time given for the realization of this project as well as for providing databases that allowed the attainment of the necessary bibliography.

Ethical disclosures

Protection of human and animal subjects. This research does not used animal nor human material.

Confidentiality of data. Not applicable

Right to privacy and informed consent. No applicable

Funding: None

Conflict of Interest

The author declares no conflict of interest.

Bibliography

47. Gramolelli S, Schulz TF. The role of Kaposi sarcoma-associated herpesvirus
55. Lawson JS, Salmons B, Glenn WK. Oncogenic Viruses and Breast Cancer: Mouse Mammary Tumor Virus (MMTV), Bovine Leukemia Virus (BLV), Human Papilloma Virus (HPV), and Epstein-Barr Virus (EBV). Front Oncol. 2018;8:1.