ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

ARTÍCULO DE REVISIÓN

The viruses in the human oncogenesis

Anggi Vélez-Bohórquez[1], Mabel Bohórquez-Lozano[2,*], Magdalena Echeverry-de-Polanco[3]

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 document 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

Los virus en la oncogénesis humana

Resumen

Con base en asociaciones epidemiológicas y experimentación, se ha logrado establecer relaciones entre los virus y el cáncer. Para los más de 14 millones de casos nuevos de cáncer por año, se estima que el 15% se relacionan con agentes virales. Se han documentado malignidades epiteliales, hematolinfoides y mesenquimales, relacionadas con diferentes virus: Epstein Barr, sarcoma de Kaposi, hepatitis B y C, linfotrófico humano tipo 1, carcinoma de Merkel y papiloma humano; se plantean nuevos virus con potencial oncogénico como citomegalovirus, poliomavirus JC y BK. La interacción de los virus con el hospedero muestra activación de oncogenes, inhibición de supresores tumorales y activación de miRNAs, como factores determinantes en el desarrollo de cáncer. La patología se inicia con la infección que induce la desregulación de la señalización celular. El virus de Epstein Barr es el prototipo oncogénico, el 1% de los tipos de cáncer humanos se relacionan con él.

Palabras Clave: Neoplasias, virología, patogénesis.

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 animals[1,2]. Later on, these "agents" were classified as viruses, giving rise to the concept of oncogenic viruses in 1970[3].

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 countries[3].

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 oncogenesis[4].

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

Cómo citar este artículo: A. Vélez-Bohórquez, *et al*. The viruses in the human oncogenesis. Infectio 2018; 22(4): 213-222

microorganism, its effects on the host, the reproducibility of these by different researchers and the epidemiological relationships[5]. 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[4].

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

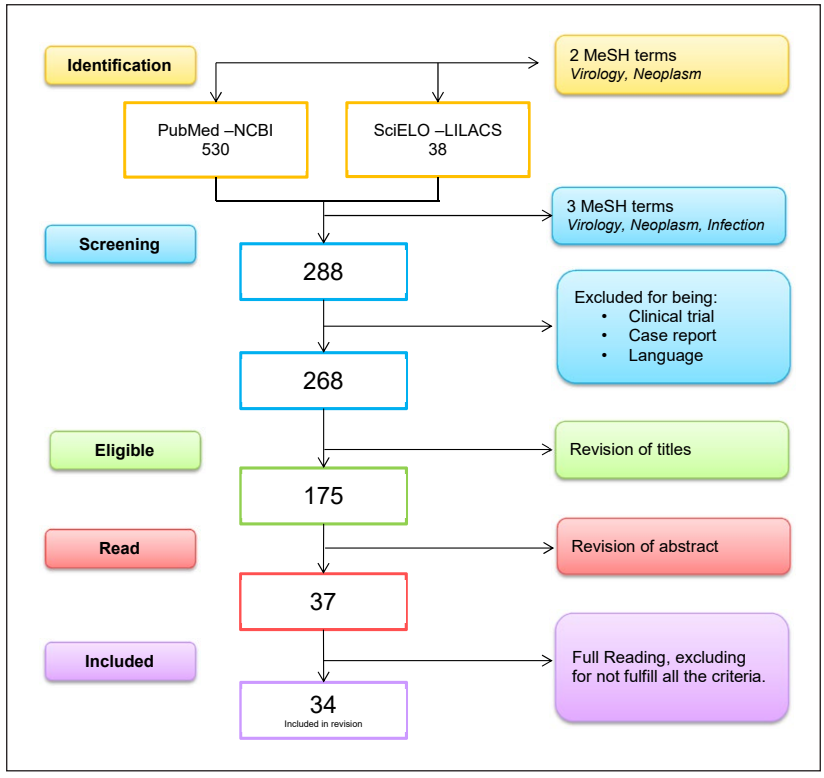

Figure 1.

Table 1. Inclusion criteria according to de acronym PICO *.

Indicators PICO	Results according to PICO
Design	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.
Population	Malignant neoplasm associated to oncogenic viruses
Intervention	None
Comparison	Scientific literature, type: systematic review. "Neoplasm", "Virology", "Related" y "Etiopathogenic"
Outcome	Classification of oncogenic viral particles and their cellular targets related to the infection and its oncogenic effects

*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 hens[6], followed by the description of oncogenic viruses in mammals in the thirties, with accelerated development in tumor virology in the subsequent decades[7]. The twentieth century culminated with Harld 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 researchs[2,8]; this announcement was recognized with the Nobel Prize in 2008[9]. 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 identified[4]. 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 DNA[4]. 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 oncogenesis[10,11]. 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 synthesis[12]. 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 3[13,14].

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 proteosomal degradation characteristic of Burkitt's lymphoma (16); 2. Type II latency, EBNA in conjunction with membrane proteins LMP-1 and 2[15]; 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 block[17,18]; 3. Type III latency associated with post-transplant lymphoproliferative disorders is associated with elevation of cellular miR155 that activates BCR, promoting proliferation[15,19].

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 BCR[20]; Through NS3 and E7, pro-inflammatory interleukins are activated that increase somatic hypermutation and genetic translocation[21], with the consequent overexpression of BLC-2 and the reduction of caspase action, causing apoptotic dysfunction. MirR122 is a miRNA specific to the liver[18,22], whose mechanism of action is still uncertain. It was described by Lin and Flemington[19] 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 transformation[23].

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 DNA[24]. 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 telomerases[25].

Viruses Related to Tumors of Epithelial Origin

Nasopharyngeal and Oropharyngeal carcinoma: it is a distinctive histological subtype of head and neck tumors, with variants such as keratinized and non-keratinizing carcinoma[26]. 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[26].

Gastric carcinoma: It has been associated with bacterial infection by *Helicobacter pylori*[27], 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%)[26]. 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[27,28]. The infection is established in its type I or II latency form[15], 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.

Genre	Genome	Virus	IARC Group	Replication	Transmission	Cellular tropism	Primary infection
Lympho-crypto-virus	Linear double-stranded DNA	EBV HHV4	1	Lytic and latency. In 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.	Saliva	B lymphocytes and epithelial cells.	Asymptomatic. Mononucleosis.
Rhadino-virus		KSHV HHV8	1		Sexual contact	B lymphocytes periphery mononuclear cells.	Asymptomatic
Orto-hepadna-virus	Circular double-stranded DNA	HBV	1	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 pregenomic RNA) and then a reverse transcriptase that encodes the viral DNA.	Sexual, parenteral	Hepatocytes	Acute hepatitis and chronic 10%.
Hepaci-virus	Single chain RNA	HCV	1	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 posteriation in the form of vesicles.	Sexual contact, parenteral	Hepatocytes, B lymphocytes, dendritic cells	Acute hepatitis and chronic 85%.
Deltaretro-virus	RNA	HTLV1	1	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.	Fluids with cells	T lymphocytes	Asymptomatic.
Polyoma-virus	Circular double-stranded DNA	MC	2A	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.	Not clear. Maybe respiratory droplets.	Epithelial cells of hair follicles, Merkel´s cells	Asymptomatic.
Papova-virus	Double-stranded DNA	VPH	1	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.	Sexual, mucosal contact.	Stratified epithelial cells	Warts, condyloma acuminatum, oral and laryngeal papillomatosis

Adapted from Sherris Medical Microbiology, 5th edition, Kenneth Ryan-George Ray, Mc Graw Hill editorial. Medical microbiology: Jawetz, Melnick and Adelberg, 25th edition, Mc Graw Hill publishing house. **IARC**: International Agency for Research on Cancer.

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

Neoplasm	Virus	Oncogenic viral particle	Cellular target/ Cellular effects	Reference
HEMATOLINFOIDE				
B-cell Lymphoma	Epstein Barr	EBNA 1	Protooncogene translocation c-MYC (8-14), proliferation.	15, 16, 19, 30
Plasmablastic lymphoma			Proinflammatory cytokines	
Burkitt lymphoma			It prevents proteosomal degradation and presentation of antigens.	
			Facilitates the union and degradation of p53	
Hodgkin lymphoma		EBNA 3C	Cell immortalization	17
T/NK-cell lymphoma		LMP1	Active p13K y BCR. Deregulation of apoptotic pathways: JAK y JNK	15, 16, 17, 18
			Deregulation of proliferation: MAP-Kinasa	17
			NK cell activator	15, 16, 30
Leukemia/ Adult T-cell lymphoma			miR155, miR146: induces uncontrolled proliferation	16, 18, 19, 29
			miR21: down-regulation of tumor suppressors	16, 18,19
B-cell Lymphoma	Hepatitis C	E2	Bind to CD81 that activates CD19-CD21 and proliferation	19,20
Marginal zone lymphoma		Unknown	miR26b: activates BCL-2 (antiapoptotic, reduces caspases activity)	
		NS3 y E7	IL2, IL-10 increases somatic hypermutation	20, 21, 65
MALT			Translocation 14-18 overexpression of BLC-2	
No Hodgkin lymphoma	Herpes 8	vCyc	Integrates the host genome and generates cell expansion	17, 23
Leukemia/T-cell lymphoma	HTLV-1	Tax	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	17, 24, 65
		HBZ	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.	24
EPITELIAL				
Nasopharyngeal carcinoma	Epstein Barr	EBNA 1	Protooncogene translocation c-MYC (8-14), proliferation.	15, 30
Gastric carcinoma			DNA metilation and suppression of p16	15, 27
Lymphoepithelial carcinoma		LMP1	Activate p13K y BCR. Deregulation of apoptotic pathways: JAK y JNK	26, 30
			Deregulation of proliferation: MAP-Kinasa	15, 30
Hepatocellular carcinoma	Hepatitis B and C	Pre-S2 deletion mutant proteins	TGF-β, IL1-β y TNF-α active JNK that increases the rate of cell proliferation	31, 34
		STAT3 y NF-kB	Antiapoptotic and regulate tumor angiogenesis	32
		Viral protein HBx	Activates mitogenic signals, generates chromosomal instability, increased metalloproteinase matrix production, which facilitates cell migration	4, 32, 33
		Viral protein HBVs	Mitochondria: inhibits JTB by increasing the life of the cell and preventing apoptosis	41
		Unknown	miR602: inactivation RASSF1A	19
	Hepatitis C	FNDC3B	Codifies a product that facilitates cell motility and metastasis	36
Merkel carcinoma	Merkel	T (large) antigen	Bind pRB, active proliferation	5, 38
		T (small) antigen	It binds and reprograms PP2A, promotes cell cycle and transformation.	
Cervical	HPV	E6	Degrade p53, with deregulation	39, 41, 43
Skin: Baso- and Squamous-cell carcinoma		E7	Degrade pRB	39, 43
Oropharyngeal Carcinoma			Suppression of miR203 that activates TP63 by promoting proliferation	19
Squamous neoplasm of the ocular surface			Induces telomerase activity, increasing the life of keratinocytes	9
		Unknown	miR100: inhibits PLK1 gene, promotes early carcinogenesis	19, 43

Neoplasm	Virus	Oncogenic viral particle	Cellular target/ Cellular effects	Reference
MESENQUIMAL				
Leiomyo-sarcoma	Epstein Barr	EBNA 1	Protooncogene translocation c-MYC (8-14), proliferation.	5, 19, 30, 62
Follicular dendritic				
Mesenchymal neoplasm				
Kaposi Sarcoma	Herpes 8 - Kaposi	LANA-1	Inhibit p53 y pRB	47, 49
		Prox-1	Causes lymphoendothelial differentiation.	
		vFLIP,	Induces endothelium-mesenchymal transition. Responsible for fusiform morphology.	
		kaposins A, B, C y ORF K1	Tumorogenesis promoter	
		miR-K12-1	Arrest p53	19
		miR-K12-3 y miR-K12-7	Active secretion of IL6 and IL10, which promote cell growth, angiogenesis and suppression of T cells.	19

Lymphoepithelial carcinoma: It is a poorly differentiated carcinoma with dense lymphocytic infiltrate[26]. It has been described in locations such as stomach, esophagus, tonsils, salivary glands, parotid[29], thymus, lungs and intrahepatic biliary epithelium[30]. The poor differentiation of these epithelial cells and an inflammatory environment are the oncogenic characteristics of the Epstein Barr virus, characterized by type II latency that interrupts multiple cellular processes and signaling pathways mentioned above.

Hepatocellular carcinoma (HCC): This carcinoma has low development associated with fibrosis. Epidemiologically it has been related in 80% of the cases with the chronic infection by the Hepatitis B (HBV) and the Hepatitis C virus (HCV), turning the infection into one of the most important risk factors. In the natural process of viral hepatitis, cirrhosis is not reached until 20 years after infection and oncogenesis takes at least 10 more years[31]. These viruses are widely distributed throughout the world and have a range of oncogenic mechanisms[32] as follows:

a. The inflammatory microenvironment that promotes the activation of the transforming growth factor beta (TGF-β) stimulates mitogenic factors such as JNK (of the MAPK family), producing rapid cell division with decreased genetic repair. Other endogenous inflammatory products such as IL- 1β, TNF-α and IL-6 (which generate resistance to apoptosis), are capable of activating these pathways. TGF-β maintains a relationship with pSmad3C under normal conditions, but when the latter is persistently phosphorylated, a mitogenic effect occurs and inhibits the apoptosis of transformed cells, a critical step for the progression of malignancy[31].
b. The induction of oxidative damage in lipids, mitogenic proteins such as MAPL, P13K, p53 and β-catenin, and in DNA. These reactive oxygen species induce intracellular calcium signaling, which increases their mitochondrial concentrations by activating STAT3 as antiapoptótico[32].
c. The insertion of viral DNA into the genome of the host in early stages of infection, which in some cases results in major genetic alterations, such as genomic instability, deletions, amplifications and chromosomal translocations. Multiple studies have described common integration sites, generally close to segments that control proliferation, survival, differentiation and immortalization, with advantages for tumorigenesis such as production of mutated HBx and mutated PreS2[32].
d. The products of the virus like Hbx and PreS / S. Hbx is a viral protein that activates aforementioned mitogenic factors. It also binds directly to p53 inhibiting apoptosis; it has been identified as a paracrine activator of stellate cell activation, promotes cell migration by increasing intracellular metalloproteinase and angiogenesis when activating HIF1 that activates VEGF and ANG2[32]. 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 polyploidy and inhibits JTB by increasing cell motility, facilitating metastasis[32,33]. PreS2 also interacts with c-Jun and hyperphosphorylates pRB[34].
e. The aberrant methylation of promoter areas (CpG islands), which inactivate tumor suppressors in early stages of the disease. The enzyme DNMT is in charge of maintaining methylation patterns of the cell, with an up-regulation of this enzyme by Hbx. It has a preference for methylation near tumor suppressors such as RASSF1A, p16, p21, as well as adhesion controllers cellular such as E-cadherin, which, when inhibited, facilitates tumor metastasis[32].

The control of the microRNAs: Multiple interaction between the virus and these non-coding particles[22] 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[19]. HBV and HCV share multiple mechanisms of transformation and tumorigenesis, with small diffe-

rences; one of them is the inhibition of the tumor suppressor of promyelocytic leukemia (PML)[35,36]. This possesses nuclear domains (PML-NBs), involved in the regulation of apoptosis, cellular senescence and antiviral response. It has been shown that HCV nuclear proteins interfere with multiple regulatory host particles including p53 by attacking their coactivator PML.

Merkel's carcinoma: This is one of the most aggressive and lethal types of skin cancer in up to 30% of patients. It occurs mostly in immunocompromised patients[37]. In 2008 its relationship with the virus of the polyomaviridae family was found. The Merkel cell carcinoma virus (MCV) has two oncoproteins; the long T (LT), which binds to pRB stimulating proliferation and the small T protein (Ts) which binds and reprograms the PP2A protein, to induce cell cycle progression and transformation. It also activates cell translocation factors such as 4E-BP1 that favor integration and genetic instability[37,38].

Oropharyngeal squamous cell carcinoma: This is a unique clinical entity, characterized by the anatomical location in the junction of soft and hard palate to the hyoid bone, including the base of the tongue It is associated with the human papilloma virus (HPV). It affects a heterogeneous population with determined risk factors and it is related to high-risk serotypes (HPV 16 and 18)[39] such as cervical carcinoma[40]. The virus has a common pathogenic pathway characterized by an advance in malignancy in which each time there is amount of virus present. Dysplastic changes are found in early stages, followed by carcinomas in situ, to culminate in infiltration of squamous cell carcinoma. It is noteworthy that oropharyngeal cancers are reported with viral changes for HPV 6 and 11, usually considered low risk. It is postulated that their behavior is not associated with benignity in this location[39].

The HPV has certain viral proteins with different functions during the infection and progression of the disease. E1 is essential for cellular regulation and thus, it supports viral replication. E2 is inactivated to increase the number of viral and epithelial cells with the integrated viral genome. The viral oncoproteins E6 and E7 cause genomic instability by coupling to the host genome and inactivate and/or reduce the half-life of p53 and pRB respectively. This translates into a lack of control during the cell cycle and the activation of cell signaling that causes uncontrolled cellular differentiation and proliferation by increasing the activity of p16[41,42]. The oncoproteins in turn have effects on the miRNA. E7 suppresses the activity of miR203 in epithelial cells, promoting proliferation and it is believed to facilitate viral replication, forcing the cell into the S phase, where the viral DNA is easily amplified[39]. E6 inhibits miR219 which overstimulates the LAMB3 gene involved in cell migration and tumorigenesis[17]. Pedroza et. al, relates other microRNAs related to early carcinogenesis, such as miR100, which promotes the activation of the PLK1 gene that promotes early carcinogenesis, as well as miR10a, miR196a and miR132 that are upregulated and contribute to cell transformation through the HOX and miR886-5p overexpression. This inhibits the process of apoptosis through the BAX gene[43].

The HPV has also been associated with squamous neoplasms of the ocular surface (pterygium, papilloma, carcinoma in situ, conjunctival intraepithelial neoplasia), which comprise the same phases of pre-malignancy and malignancy[44] and an oncogenic pathway similar to that previously described. However, the clinical evidence reported is scarce and is basically explained by two mechanisms: suboptimal study designs and techniques to identify HPV in biological specimens[45].

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[46] 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[9].

Tumors of Mesenchymal Origin

There are multiple presentations of this type of malignancy, such as leiomyosarcoma, follicular dendritic cell sarcoma and myopericytoma[30] that have been related to the Epstein Barr virus and the nuclear antigen EBNA-1, which mediates oncogenesis, mainly by the translocation of the c-MYC protooncogene and the subsequent proliferation.

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[47,48]. 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[49]. 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[19].

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[5,50,51]. Among them, the Cytomegalovirus of the herpesviridae family are found as potential causal agents of CNS malignancies (gliomas and multiform glioblastoma)[52], colon and prostate carcinoma[53,54]. JC and BK viruses of the polyomaviridae family are causal agents of tumors of the central nervous system[1,54] and colorectal carcinoma[50]. The postulated mechanisms for tumorigenesis are explained in Table 4. There has been descri-

Table 4. Viruses and possible oncogenic mechanism, without enough evidence.

Neoplasm	Virus	Oncogenic viral particle	Cellular target/ Cellular effects	Reference
Glioma	Cytomegalovirus	Prolonged infection of monocytes and macrophages.	TAMs, releasers of IL6, IL10 TGF-β, that activate proliferation by means of STAST 3	51
		Gen US3	Retention of MHC I in the endoplasmic reticulum	
		US28	Promotes cellular migration by RANTES and MCOP-1	51, 54
Colon Carcinoma		UL 3	It binds to caspase-8 and inhibits Fas-mediated apoptosis.	51
		UL37	Inhibits proapototic pathways, Bax and Bak.	51, 54
Prostate Carcinoma		Gen UL83	Produces ppg65 that blocks the presentation of antigens	51
		IE1	Mutagenics, break into DNA repair interfering with RM and ATR.	
			Delete p53 and pRb	
		IE2	Disable p53	
		mirR-UL112	Suppress the expression of MHC I	
Glioblastoma multiforme		RNABeta 2.7	Mitochondria, prevents apoptosis.	
		UL36	Inhibits Fas-mediated apoptosis	54
		UL123/124	Inhibits apoptosis by activating PI3 kinase.	
		Unknown	Stimulates hTERT increases the activity of telomerase	
		Unknown	Induces CD40 expression by increasing proliferation cell signaling	
Oligo-dendorglioma, astrocytoma, ependymoma, medullo-blastoma.	Polyomavirus (JC y BK)	TAG	Inhibits Rb, releasing E2F. Inhibits p53	54
		tAG	Deregulates WTN of β-catenin and stimulates gene expression.	
			Activates PP2A, affects the cytoskeleton and promotes migration.	

be another virus linked to the development of breast cancer like bovine leukemia virus (BLV), mouse mammary tumor-like virus (MMTV) both retroviruses[55] their oncogenic mechanism still no clear, there is substantial information, but cannot be regarded as conclusive[56] 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 system[58], not even this association are no documented properly.

Discusion

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 metastasis[59,60]. These provide proliferative advantages even under conditions of nutrients and poor oxygen[61].

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 agents[7,30,62].

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 33[63]. In the near future, specific treatments should be implemented, perhaps through vectors of genetic therapies or by the use of oncolytic therapy agents[64,65].

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 do 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

1. Reyes KR, M. Virus oncogénicos. Revista cubana de genética comunitaria. 2013;7(2):9.
2. Orth G, Jablonska S, Favre M, Croissant O, Obalek S, Jarzabek-Chorzelska M, et al. Identification of papillomaviruses in butchers' warts. J Invest Dermatol. 1981;76(2):97-102.
3. IARC IAFROC. GLOBOCAN_2012: WHO; 2015 [Available from: http://www.iarc.fr/en/feeds/index.php.
4. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat Rev Cancer. 2010;10(12):878-89.
5. Moore PS, Chang Y. The conundrum of causality in tumor virology: the cases of KSHV and MCV. Semin Cancer Biol. 2014;26:4-12.
6. Rubin H. The early history of tumor virology: Rous, RIF, and RAV. Proc Natl Acad Sci U S A. 2011;108(35):14389-96.
7. Jung J, Munz C. Immune control of oncogenic gamma-herpesviruses. Curr Opin Virol. 2015;14:79-86.
8. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009;384(2):260-5.
9. Quint KD, Genders RE, de Koning MN, Borgogna C, Gariglio M, Bouwes Bavinck JN, et al. Human Beta-papillomavirus infection and keratinocyte carcinomas. J Pathol. 2015;235(2):342-54.
10. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res. 2014;2014:149185.
11. Morales-Sanchez A, Fuentes-Panana EM. Human viruses and cancer. Viruses. 2014;6(10):4047-79.
12. Jia LT, Zhang R, Shen L, Yang AG. Regulators of carcinogenesis: emerging roles beyond their primary functions. Cancer Lett. 2015;357(1):75-82.
13. WHO IAfRoC-. LIST OF CLASSIFICATIONS, VOLUMES 1–119: WHO; 2016 [Available from: http://monographs.iarc.fr/ENG/Classification/latest_classif.php.
14. Pearce N, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, et al. IARC monographs: 40 years of evaluating carcinogenic hazards to humans. Environ Health Perspect. 2015;123(6):507-14.
15. Grywalska E, Rolinski J. Epstein-Barr virus-associated lymphomas. Semin Oncol. 2015;42(2):291-303.
16. Vockerodt M, Yap LF, Shannon-Lowe C, Curley H, Wei W, Vrzalikova K, et al. The Epstein-Barr virus and the pathogenesis of lymphoma. J Pathol. 2015;235(2):312-22.
17. Sadrzadeh H, Abtahi SM, Fathi AT. Infectious pathogens and hematologic malignancy. Discov Med. 2012;14(79):421-33.
18. Hatton OL, Harris-Arnold A, Schaffert S, Krams SM, Martinez OM. The interplay between Epstein-Barr virus and B lymphocytes: implications for infection, immunity, and disease. Immunol Res. 2014;58(2-3):268-76.
19. Lin Z, Flemington EK. miRNAs in the pathogenesis of oncogenic human viruses. Cancer Lett. 2011;305(2):186-99.
20. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol. 2013;59(1):169-77.
21. Carbone A, Gloghini A. Relationships between lymphomas linked to hepatitis C virus infection and their microenvironment. World J Gastroenterol. 2013;19(44):7874-9.
22. Qiao DD, Yang J, Lei XF, Mi GL, Li SL, Li K, et al. Expression of microRNA-122 and microRNA-22 in HBV-related liver cancer and the correlation with clinical features. Eur Rev Med Pharmacol Sci. 2017;21(4):742-7.
23. Dittmer DP, Damania B. Kaposi sarcoma associated herpesvirus pathogenesis (KSHV)--an update. Curr Opin Virol. 2013;3(3):238-44.
24. Bangham CR, Cook LB, Melamed A. HTLV-1 clonality in adult T-cell leukaemia and non-malignant HTLV-1 infection. Semin Cancer Biol. 2014;26:89-98.
25. Zhao T, Matsuoka M. HBZ and its roles in HTLV-1 oncogenesis. Front Microbiol. 2012;3:247.
26. Tsao SW, Tsang CM, To KF, Lo KW. The role of Epstein-Barr virus in epithelial malignancies. J Pathol. 2015;235(2):323-33.
27. Matsusaka K, Funata S, Fukayama M, Kaneda A. DNA methylation in gastric cancer, related to Helicobacter pylori and Epstein-Barr virus. World J Gastroenterol. 2014;20(14):3916-26.
28. Doolittle JM, Webster-Cyriaque J. Polymicrobial infection and bacterium-mediated epigenetic modification of DNA tumor viruses contribute to pathogenesis. MBio. 2014;5(3):e01015-14.
29. Santamaria AD, B.; García, L.; Verdaguer, J. Carcinoma linfoepitelial primario de glándula parótida. Revista española de cirugía oral maxilofacial. 2013;35(2):2.
30. Michelow P, Wright C, Pantanowitz L. A review of the cytomorphology of Epstein-Barr virus-associated malignancies. Acta Cytol. 2012;56(1):1-14.
31. Murata M, Yoshida K, Yamaguchi T, Matsuzaki K. Linker phosphorylation of Smad3 promotes fibro-carcinogenesis in chronic viral hepatitis of hepatocellular carcinoma. World J Gastroenterol. 2014;20(41):15018-27.
32. Tarocchi M, Polvani S, Marroncini G, Galli A. Molecular mechanism of hepatitis B virus-induced hepatocarcinogenesis. World J Gastroenterol. 2014;20(33):11630-40.
33. Pollicino T, Saitta C. Occult hepatitis B virus and hepatocellular carcinoma. World J Gastroenterol. 2014;20(20):5951-61.
34. Su IJ, Wang LH, Hsieh WC, Wu HC, Teng CF, Tsai HW, et al. The emerging role of hepatitis B virus pre-S2 deletion mutant proteins in HBV tumorigenesis. J Biomed Sci. 2014;21:98.
35. Herzer K, Weyer S, Krammer PH, Galle PR, Hofmann TG. Hepatitis C virus core protein inhibits tumor suppressor protein promyelocytic leukemia function in human hepatoma cells. Cancer Res. 2005;65(23):10830-7.
36. Herzer K, Gerken G, Hofmann TG. Hepatitis C-associated liver carcinogenesis: role of PML nuclear bodies. World J Gastroenterol. 2014;20(35):12367-71.
37. Chang Y, Moore PS. Merkel cell carcinoma: a virus-induced human cancer. Annu Rev Pathol. 2012;7:123-44.
38. Spurgeon ME, Lambert PF. Merkel cell polyomavirus: a newly discovered human virus with oncogenic potential. Virology. 2013;435(1):118-30.
39. Miller DL, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus)-associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-53.
40. Schiffman M, Wentzensen N. Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(4):553-60.
41. Martinez AB, R.; Díaz A. . Infección por papiloma virus humano y carcinoma escamocelular bucal, diversas técnicas moleculares para detectar su presencia. AVANCES EN ODONTOESTOMATOLOGÍA. 2014;30(2):10.
42. Tomaic V. Functional Roles of E6 and E7 Oncoproteins in HPV-Induced Malignancies at Diverse Anatomical Sites. Cancers. 2016;8(10).
43. Pedroza-Torres A, Lopez-Urrutia E, Garcia-Castillo V, Jacobo-Herrera N, Herrera LA, Peralta-Zaragoza O, et al. MicroRNAs in cervical cancer: evidences for a miRNA profile deregulated by HPV and its impact on radio-resistance. Molecules. 2014;19(5):6263-81.
44. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ. Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res. 2014;129:172-82.
45. Di Girolamo N. Association of human papilloma virus with pterygia and ocular-surface squamous neoplasia. Eye (Lond). 2012;26(2):202-11.
46. Reusser NM, Downing C, Guidry J, Tyring SK. HPV Carcinomas in Immunocompromised Patients. J Clin Med. 2015;4(2):260-81.
47. Gramolelli S, Schulz TF. The role of Kaposi sarcoma-associated herpesvirus

in the pathogenesis of Kaposi sarcoma. J Pathol. 2015;235(2):368-80.
48. De Paoli P, Carbone A. Kaposi's Sarcoma Herpesvirus: twenty years after its discovery. Eur Rev Med Pharmacol Sci. 2016;20(7):1288-94.
49. Gantt S, Casper C. Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. Curr Opin Infect Dis. 2011;24(4):295-301.
50. De Paoli P, Carbone A. Carcinogenic viruses and solid cancers without sufficient evidence of causal association. Int J Cancer. 2013;133(7):1517-29.
51. Soroceanu L, Cobbs CS. Is HCMV a tumor promoter? Virus Res. 2011;157(2):193-203.
52. Wang L, Yang M, Liao S, Liu W, Dai G, Wu G, et al. Hsa-miR-27b is up-regulated in cytomegalovirus-infected human glioma cells, targets engrailed-2 and inhibits its expression. Exp Biol Med (Maywood). 2017:1535370217699535.
53. Iwahori S, Umana AC, VanDeusen HR, Kalejta RF. Human Cytomegalovirus v-CDK UL97 Phosphorylates and Inactivates the Retinoblastoma Protein-Related p107 and p130 Proteins. J Biol Chem. 2017.
54. Saddawi-Konefka R, Crawford JR. Chronic viral infection and primary central nervous system malignancy. J Neuroimmune Pharmacol. 2010;5(3):387-403.
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.
56. Lawson JS, Glenn WK. Multiple oncogenic viruses are present in human breast tissues before development of virus associated breast cancer. Infect Agent Cancer. 2017;12:55.
57. Drop B, Strycharz-Dudziak M, Kliszczewska E, Polz-Dacewicz M. Coinfection with Epstein-Barr Virus (EBV), Human Papilloma Virus (HPV) and Polyoma BK Virus (BKPyV) in Laryngeal, Oropharyngeal and Oral Cavity Cancer. Int J Mol Sci. 2017;18(12).
58. Guidry JT, Scott RS. The interaction between human papillomavirus and other viruses. Virus Res. 2017;231:139-47.
59. Mushtaq M, Darekar S, Kashuba E. DNA Tumor Viruses and Cell Metabolism. Oxid Med Cell Longev. 2016;2016:6468342.
60. Nikitin PA, Luftig MA. The DNA damage response in viral-induced cellular transformation. Br J Cancer. 2012;106(3):429-35.
61. Noch E, Khalili K. Oncogenic viruses and tumor glucose metabolism: like kids in a candy store. Mol Cancer Ther. 2012;11(1):14-23.
62. Daskalogianni C, Pyndiah S, Apcher S, Mazars A, Manoury B, Ammari N, et al. Epstein-Barr virus-encoded EBNA1 and ZEBRA: targets for therapeutic strategies against EBV-carrying cancers. J Pathol. 2015;235(2):334-41.
63. Stanley M. Tumour virus vaccines: hepatitis B virus and human papillomavirus. Philos Trans R Soc Lond B Biol Sci. 2017;372(1732).
64. Belcaid Z, Lamfers ML, van Beusechem VW, Hoeben RC. Changing faces in virology: the dutch shift from oncogenic to oncolytic viruses. Hum Gene Ther. 2014;25(10):875-84.
65. Fan H, Johnson C. Insertional oncogenesis by non-acute retroviruses: implications for gene therapy. Viruses. 2011;3(4):398-422.