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Study of viruses associated with cancer diseases

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وزارة التعليم العالي والبحث العلمي
كلية الحلة الجامعة الاهلية
قسم تقنيات التحليلات المرضية

دراسة الفيروسات المرتبطة بأمراض السرطان

بحث مقدم إلى كلية الحلة الجامعة ضمن متطلبات الحصول على شهادة البكلوريوس في تكنولوجيا المختبرات الطبية

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بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)

صدق الله العظيم

«سورة المجادلة: الآية 11».

Dedication

I dedicate this work of my work to the one who taught me to give, to the one whose name I carry with all pride, and I hope that God will extend his life to see fruits that have come to be harvested after a long wait.

"My dear father"

To my companions in life, to the meaning of love, tenderness and devotion, to the smile of life and the secret of existence, to whom Her prayers were the secret of my success, my dearest friends

"My beloved mother"

To those who had great credit for encouraging and motivating me, and from whom I learned perseverance and diligence, to those who mattered and on whom I relied, and through whose presence I gained limitless strength and love, to those with whom I learned the greater meaning of life.

"My brothers and sisters"

To those who showed brotherhood and were distinguished by loyalty and giving. To those who accompanied them on the happy and sad paths of life. I walked to those who were with me on the path to success.

With God’s success and prayers from my mother, there are only a few steps left to finish my career. Thank you to everyone who extended a helping hand to me

Acknowledgments

I thank God Almighty first and foremost for the great grace that He has bestowed upon me, then I thank those who favored them. My beloved parents do not cease to me for all their efforts from the moment of my birth to these blessed moments. For everyone who advised me, guided me in preparing this research . And I especially thank the distinguished “Dr. Ruqaya Yahya Abd AL-Shaheed”, for helping me Supporting me and guiding me with advice, education, correction, and all that she did with me .

I am extremely thankful to the dean of Al-Hilla University College and chairman of the department of Medical Laboratory for their cooperation during the work.

Abstract:

The study included types of viruses that contribute to the development of cancer ,The first human tumor virus was discovered in the middle of the last century by Anthony Epstein, Bert Achong and Yvonne Barr in African pediatric patients with Burkitt's lymphoma. To date, seven viruses -EBV, KSHV, high-risk HPV, MCPV, HBV, HCV and HTLV1- have been consistently linked to different types of human cancer, and infections are estimated to account for up to 20% of all cancer cases worldwide. Viral oncogenic mechanisms generally include: generation of genomic instability, increase in the rate of cell proliferation, resistance to apoptosis, alterations in DNA repair mechanisms and cell polarity changes, which often coexist with evasion mechanisms of the antiviral immune response. Viral agents also indirectly contribute to the development of cancer mainly through immunosuppression or chronic inflammation, but also through chronic antigenic stimulation. There is also evidence that viruses can modulate the malignant properties of an established tumor. In the present work, causation criteria for viruses and cancer will be described, as well as the viral agents that comply with these criteria in human tumors, their epidemiological and biological characteristics, the molecular mechanisms by which they induce cellular transformation and their associated cancers.

الخلاصة:

شملت الدراسة انواع الفايروسات التي تساهم في تطوير السرطان , وتم اكتشاف أول فيروس ورم بشري في منتصف القرن الماضي على يد أنتوني إبستين وبيرت أشونغ وإيفون بار في مرضى الأطفال الأفارقة المصابين بسرطان الغدد الليمفاوية بوركيت. حتى الآن، تم ربط سبعة فيروساتEBV - ، وKSHV، و HPVعالي الخطورة، وMCPV، وHBV، وHCV، و - HTLV1بشكل ثابت بأنواع مختلفة من السرطان البشري، وتشير التقديرات إلى أن العدوى تمثل ما يصل إلى 20٪ من جميع حالات السرطان في جميع أنحاء العالم . تشمل الآليات الفيروسية المسببة للسرطان عمومًا ما يلي: توليد عدم الاستقرار الجينومي، وزيادة معدل تكاثر الخلايا، ومقاومة موت الخلايا المبرمج، والتغيرات في آليات إصلاح الحمض النووي وتغيرات قطبية الخلية، والتي غالبًا ما تتعايش مع آليات التهرب من الاستجابة المناعية المضادة للفيروسات. تساهم العوامل الفيروسية أيضًا بشكل غير مباشر في تطور السرطان بشكل رئيسي من خلال كبت المناعة أو الالتهاب المزمن، ولكن أيضًا من خلال التحفيز المستضدي المزمن. هناك أيضًا أدلة على أن الفيروسات يمكنها تعديل الخصائص الخبيثة للورم الموجود. في العمل الحالي، سيتم وصف معايير السببية للفيروسات والسرطان، بالإضافة إلى العوامل الفيروسية التي تتوافق مع هذه المعايير في الأورام البشرية، وخصائصها الوبائية والبيولوجية، والآليات الجزيئية التي تحفز من خلالها التحول الخلوي والسرطانات المرتبطة به.

Contents

List of Figures

1. Introduction

The first observations about a possible infectious etiology of cancer arose at the beginning of the past century.

Yvonne Barr observed viral particles in cell cultures from African pediatric patients with Burkitt's lymphoma; this virus was named Epstein Barr virus (EBV) in honor of their discoverers.[4] Currently, there is clear evidence that several viruses are oncogenic to humans . Ex, EBV, Kaposi's sarcoma-associated herpesvirus (KSHV), human highrisk papillomaviruses (HPV), Merkel cell polyomavirus (MCPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Human T-cell Lymphotropic virus type 1 (HTLV1) have been classified as type 1 carcinogenic agents (the most strongly associated with human cancers).[7;5,6]

Oncogenic viruses generally maintain chronic infections in which there is not or little production of viral particles, and that last for the whole life of the infected individual. These mechanisms of viral persistency and/or latency are biologically compatible with the carcinogenic process, because they avoid cell death most common in acute lytic infections, while maintaining the infectious agent hidden from the immune system. Viral persistence in the host is achieved by integrating the viral genome into the cell genome or by expressing viral proteins that equally segregate the viral genome into daughter cells during cell partitioning[13,14].

For instance, inactivation of p53 and pRb tumor suppressor genes is an event that occurs in most pathways of viral oncogenesis, both human and animal–100] .[102Increased rate of mutations are observed in the variable regions of heavy and light chains after EBV infection [136].and Telomere shortening and cell senescence are the natural consequence of unlimited cell proliferation, and tumor viruses also display mechanisms of telomere maintenance. Telomere length maintenance is a fine regulated mechanism involving a complex set of proteins and the enzyme telomerase [143].Tumor viruses interference with DNA repair mechanisms and concomitant genomic instability may be in great measure a consequence of bypassing regulatory checkpoints of telomere length and p53- and pRb-dependent senescence [148]. In this scenario, tumor viruses have evolved with these mechanisms in order to achieve replicative immortality and thus persistency.

The Aim of study :

The aim of the study is to reveal the role of the tumors viruses in canser patients .The objective of this study are :

1-Identify the types of viruses that cause tumors such as KSHV, high-risk HPV, MCPV, HBV, HCV and HTLV1- and Epstein Barr Virus in patients infection.
2- Investigate the role of viruses in influencing the immune response through a variety of mechanisms.

3-Identify the mechanisms used by viruses that disable the surveillance mechanisms that normally recognize and extinguish such abnormal cells.

2-Literature Review (Historical and Epidemiological Aspects):

The first observations about a possible infectious etiology of cancer arose at the beginning of the past century. Ellermann and Bang in 1908 and Rous in 1911 transmitted avian leukemias and sarcomas, respectively, through cell-free tumor extracts, suggesting a viral etiology [1–3]. About 50 years later, the first human tumor virus was discovered. Sir Anthony Epstein, Bert Achong and Yvonne Barr observed viral particles in cell cultures from equatorial African pediatric patients with Burkitt's lymphoma; this virus was named Epstein Barr virus (EBV) in honor of their discoverers [4].

Currently, there is clear evidence that several viruses are oncogenic to humans and the first century of tumor virology research has culminated with the Medicine Nobel Price granted to Harald zur Hausen for the discovery of HPV as the causative agent of cervical cancer [5,6]. To date, EBV, Kaposi's sarcoma-associated herpesvirus (KSHV), human highrisk papillomaviruses (HPV), Merkel cell polyomavirus (MCPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Human T-cell Lymphotropic virus type 1 (HTLV1) have been classified as type 1 carcinogenic agents (the most strongly associated with human cancers) by the International Agency for Research on Cancer (IARC) (reviewed in [7]). It is estimated that infections are responsible for up to 15% of cancer cases worldwide and about 20% in developing countries [8].

With advent of new technologies allowing genetic identification, it is very likely that this numbers will continue to increase. Virus-mediated oncogenesis results from the cooperation of multiple events, including different mechanisms bound to the viral life cycle. For example, EBV resides in B-lymphocytes that reactivate in the epithelium of the upper digestive tract and EBV has been associated to B-cell lymphomas and carcinomas in tongue, nasopharynx and stomach. [12]. Arguable, the most powerful tool to indicate direct association is the viral monoclonal analysis in the tumor; the presence of a specific viral variant or viral quasispecie in all tumor cells indicates that the event of infection preceded the malignant cell transformation.

3-Viral Oncogenic Mechanisms

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

mechanisms ensure that the virus is not lost during cellular replication. Viral persistence is usually characterized by expression of proteins that control cell death and proliferation; in this manner, oncogenic viruses nurture infection of a controlled number of cells establishing a balance between virus and host, preserving the integrity of both. Cell transformation is probably not an evolutionary viral strategy, but rather a biological accident that rarely occurs in the virus-host interaction. Cancer leads to the death of the host, and thus, it also represents the end of the virus. The existence of viral oncogenes is explained as part of the viral persistence mechanisms, which only under altered conditions may lead to cancer. All virus-associated tumors result from the cooperation of various events, involving more than persistent infection and viral transformation mechanisms. Additional oncogenic hits are necessary for full-blown transformation. The occurrence of mutations impairing expression and function of viral and/or cellular oncogenes is necessary in the carcinogenic process, in line with that, an increased mutation rate of infected over normal cells is frequently observed [13,14].

In this scenario, latently infected cells by oncogenic viruses might be more susceptible targets of additional oncogenic hits; e.g., due to smoking, a diet scarce in fruits and vegetables or/and increased exposure to environmental oncogenic agents. All these insults, plus the host genetic component driving inflammatory responses triggered by the infection itself result in cell transformation and cancer development.

3.1 .Direct and Indirect Viral Carcinogenesis

Infectious agents can contribute to carcinogenesis by direct and/or indirect mechanisms (Figure 1). The direct-acting carcinogenic agents are generally found in a monoclonal form within the tumor cells.These agents help to keep the tumor phenotype through expression of either viral or cellular oncogenes [7]. Retroviruses, whose replication cycle requires the integration of the viral genome into the host genome, commonly transform because integration deregulates expression of cellular oncogenes or tumor suppressor genes .On the other hand, EBV is an example of a virus that does not need to integrate and transforms through expression of its own oncogenes.

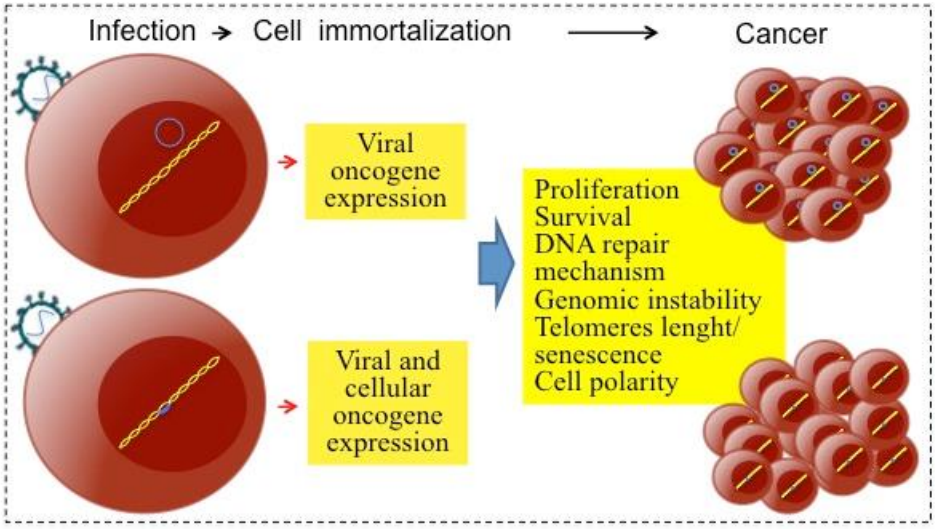

Figure 1:Direct mechanisms of viral carcinogenesis. After infecting target cells, tumor viruses are persistently maintained as genetic elements; viral genomes can form episomes (upper panel example, herpesviruses) or integrate into the host genomic DNA (lower panel example, retroviruses and HBV).

The indirect transforming viruses are not conditioned to exist within the cell that forms the tumor.These agents act through two main mechanisms: (i) triggering chronic inflammation and oxidative stress that persistently damage local tissues; and (ii) by producing immunosuppression that reduces or eliminates anti-tumor immune surveillance mechanisms (Figure 2) .

Among the most documented viral agents belonging to the first group are HBV and HCV; chronic inflammation produced by persistent infection associated with any of these viruses is a major risk to develop hepatocellular carcinoma (HCC) [15,16]. On the other hand, HIV belongs to the second group; patients with noncontrolled infection and low T cell counts frequently develop lymphomas associated with EBV or KSV infection.[17]

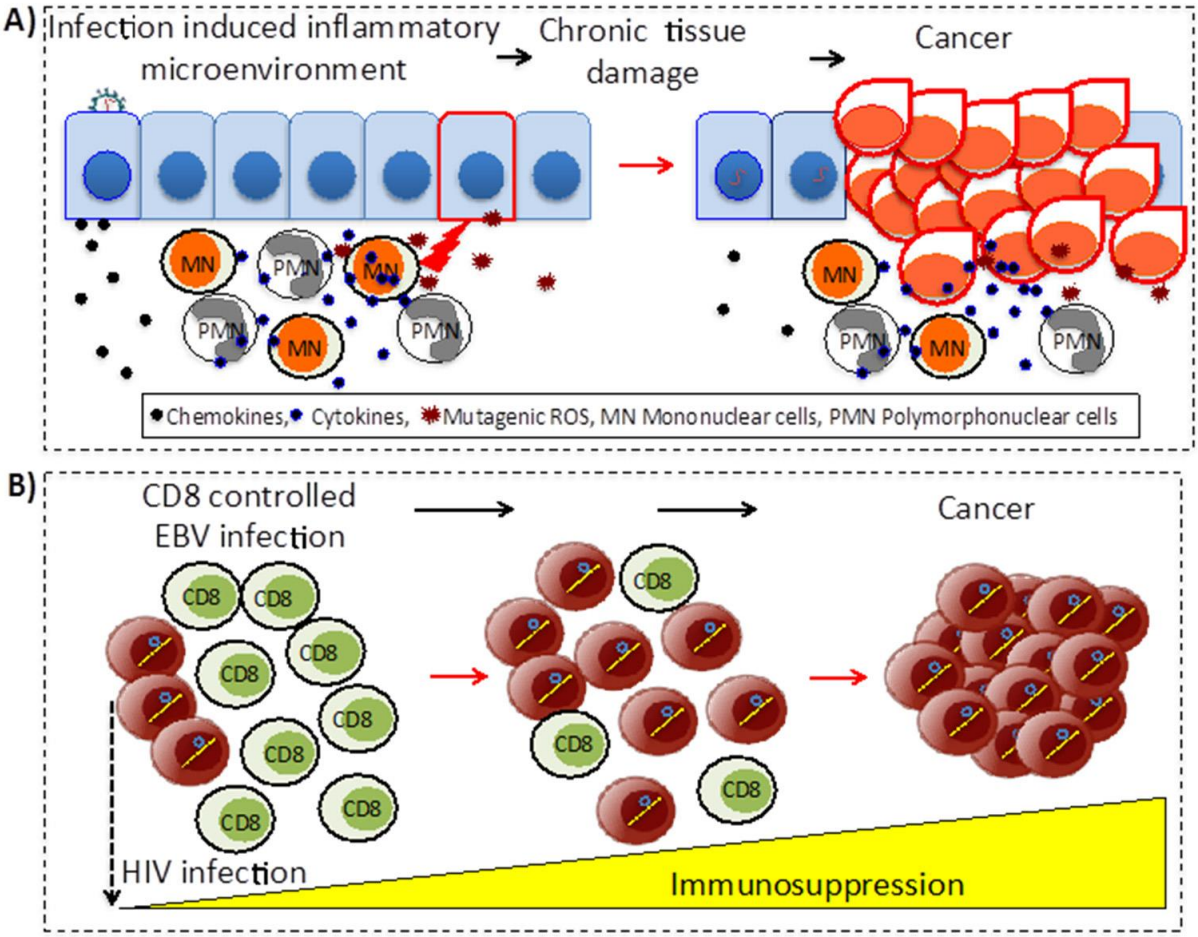

Figure 2. Indirect mechanisms of viral carcinogenesis. (A) Chronic inflammation. Infected cells produce chemokines attracting immune cells, which establish a chronic inflammatory microenvironment that persistently damage the local tissue. Cancer evolves within this cycle of infection, induced inflammation and tissue damage. (B) Immunosuppression. The prototype agent for immunosuppression is HIV. In immunocompetent individuals EBV infection is efficiently controlled by cytotoxic CD8 T cells; as HIV infection progresses and immune responses collapse, individuals become at increased risk of developing EBV associated lymphomas.

Tumorigenic viruses were previously considered either exclusively direct or indirect transforming agents. However, some agents may require both mechanisms to induce carcinogenesis; for instance HBV and HCV [15,16]. Helicobacter pylori is the prototype indirect carcinogen through chronic inflammation [18]. Nevertheless, the bacterium also encodes the CagA oncoprotein, which is translocated to epithelial cells though a type IV secretion system [19]. Therefore, direct and indirect mechanisms are not mutually exclusive and some tissues may be equally dependent in both mechanisms for oncogenic transformation, such as the liver and stomach.

4-Human Oncogenic Viruses and Associated Cancers

Many different viruses have direct transformation characteristics; The human cancers associated with viral infection are summarized

4-1- Herpesviruses: Epstein Barr Virus and Kaposi Sarcoma-Associated Herpesvirus

Herpesviruses are enveloped viruses with double-stranded linear DNA that after infecting the host cell remain in the nucleus as episomes [26]. Both EBV and KSHV show a biphasic life cycle consisting of a latent and a lytic phase. The latent phase seems to be the primary choice in which most of viral gene expression is shut down. This phase allows these viruses to coexist with the host generally asymptomatically and only in unusual situations may cause disease, e.g., during pharmacological or HIV induced immunosuppression. The lytic phase occurs in healthy individuals only in poorly understood sporadic events of reactivation. EBV, also known as HHV4 (Human Herpesvirus Type 4), is found in approximately 95% of the adult population worldwide [27]; its principal routes of transmission are oral and blood [28,29], while intrauterine transmission has been documented too [30,31].

Early acquisition of this agent does not cause disease but when primary infection occurs during adolescence or early adulthood it causes infectious mononucleosis [32]. Interestingly, this condition represents a risk factor for developing Hodgkin's lymphoma [33]. B cells are the main target of EBV infection [34]; more rarely and less understood, EBV can also infect epithelial cells, mainly in the upper digestive tract, which is thought to occur in viral reactivation events [35]. EBV has mainly been associated with malignancies of B and epithelial cells of the upper digestive tract , which provides biological plausibility and coherence to the role of EBV in these neoplasias. EBV is found in a latent stage in both lymphomas and carcinomas, and within the latent genes, there are several with oncogenic properties. The viral protein best recognized as oncogenic is LMP1, a signaling protein that imitates a constitutively active TNF receptor. LMP1 activates MAP kinases and STAT and NFκB transcription factors in B cells, and also PI3K in epithelial cells [36].

LMP1 increases proliferation and survival of the infected cell. Of note, STAT and NFκB activation potentially stimulates expression of cytokines and chemokines important to establish the inflammatory microenvironment critical to create the niche from which infectious and non-infectious tumors emerge. LMP2A is another constitutively active viral protein with ITAM (immunoreceptor tyrosine activated motif) signaling domains [37].

LMP2A expression promotes the activation of PLCγ and PI3K pathways, which correlates with its capacity to transform epithelial cells and to confer a migratory phenotype to the transformed cell [38]. LMP1 and LMP2A provide antigen recognition-like signals to B cells, required for differentiation into long-lived memory cells in which the virus persists hidden from antagonistic immune responses. Although, both proteins can be expressed in EBV-induced carcinomas, their normal function in non-lymphoid tissue is not clear. EBV-associated tumors are characterized by the expression of a different set of viral transcripts or latencies. In lymphomas arousing in immunosuppressed individuals (latency III) the family of EBNA proteins provides with additional oncogenic insults. For instance, EBNA-LP, -3A and -3C directly interfere with p53 and pRb functions, as well as with other proteins of the G0 to G1 phase transition. EBNA-1 is the common protein expressed in all EBV-associated neoplasias; it is expressed in latency III, latency II (Hodgkin's lymphoma and carcinomas) and it is the sole viral protein expressed in latency I (Burkitt's lymphoma). This absolute requirement for EBNA-1 is probably due to its capacity to equally segregate EBV episomes to both daughter cells during cell division.[39]

The prevalence of KSHV infection varies among geographic regions, being 5% in Europe, Asia and some parts of North America and more than 50% in sub-Saharan Africa. KSHV is transmitted from casual contacts as well as through sexual contact, blood transfusion and organ transplant. In non-endemic regions, the main via of transmission is probably through sexual contact and the use of contaminated syringes [40]. KSHV is the etiological agent of both lymphomas and sarcomas [41] . Neoplasias associated with KSVH were not frequent before the AIDS pandemic, but currently represent one of the most important signs of this disease.[42,43]

Several KSVH genes have potential oncogenic properties, for example, modulation of transduction of signals by K1 and K5; regulation of cell cycle by v-Cyclin and LANA 1; apoptosis inhibition by K1, vFLIP and v-Bcl2 and immune modulation by v-IRF, K3 and K5 (reviewed in [41]). LANA1 cooperates with h-Ras to transform fibroblasts and immortalize endothelial cells [44].

4.2 .High-Risk Papillomaviruses

Human papilloma viruses belong to the Papillomaviridae family; they contain a double-strand DNA genome of approximately 8000 bp and are not enveloped viruses. More than 100 members of this family have been described and from them, more than a dozen (types 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 62, 66 and 68) have been classified as high-risk due to their epidemiological association with cervical and other cancers [21]. HPV subtypes 16 and 18 are the most frequently found in tumors; the first is mainly associated with invasive cervical cancer and the second is the most frequent in squamous cell carcinoma [55,56]. Low-risk HPVs generally cause benign lesions, such as warts.[57]

HPV is transmitted by skin contact, including genital contact during sexual intercourse; thus HPV infection in the genital area tents to be common in sexually active persons. Infection is generally controlled by the immune system and only in a low number of people, HPV persists, increasing the risk to develop epithelial lesions [58]. Viral persistence seems to be greatly helped by the inability of infected cells to present antigenic epitopes to adaptive immune cells, which is common in individuals with alterations in the HLA (Human Leucocyte Antigen) antigen presentation pathway.[59]

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

in loss of E2 and over-expression of E6 and E7 [60]. Increased expression of E6 and E7 correlates with progression to high grade lesions and eventually to carcinoma in situ [58].

4.3 .Merkel Cell Polyomavirus

Polyomaviruses are non-enveloped viruses with a circular, double-stranded DNA of approximately 5000 bp. The members of this family are present in all regions of the world infecting several species. Historically, it was considered that only JCV and BKV polyomaviruses infected humans, but next generation sequencing techniques have enabled the identification of at least nine other

members in humans, among them MCPV. MCPV was identified in 2008 in an aggressive skin cancer denominated Merkel cell carcinoma (MCC) .[22]

Evidence supporting the participation of this agent in MCC carcinogenesis includes the presence of MCPV genomes in about 80% of the tumors but not in healthy tissue, and the clonal integration of the viral genome [22,61–63]. MCPV oncogenic transformation may result from loss of immune surveillance, as MCC mainly occurs in

immunosuppressed individuals. MCC was a very rare cancer before the AIDS pandemia, and today, there are around 1700 new cases per year in the US.[64,65]

The MCPV genome is inserted into the host genome during viral carcinogenesis. Integration is characterized by preserving the viral induced cell proliferation functions while abrogating viral replication; the latter probably due to deletion of some of the viral T antigen gene regions.[66,67]

Viral integration also favors host resistance to cell death promoting viral persistence in a latent state [68]. This is a significant difference between the presence of the virus in MCC and in non-tumor tissue. Due to the recent discovery of MCPV, we still do not understand the function of viral proteins. However, some viral proteins present homology in functional domains with tumorigenic polyomaviruses from non-human species. For example, like SV40 MCPV T antigens are generated by differential splicing to produce large T and small T antigens [69]. The large T antigen presents the structural motif that inactivates pRb (LXCXE) [70], and the T antigen is generally expressed in MCC, and even in its truncated form it maintains intact the pRb-inactivating domain [71]. Inactivation of the T antigen in MCC cell lines results in cell death, further supporting the causative role of MCPV in MCC [72]. Also, the small T antigen conserves the AKT/mTOR activating domain, which is responsible for loss of contact inhibition and promoting independent growth of substrate and serum [73].

4.4 .Hepatitis B Virus

The Hepadnaviridae family groups a series of viruses that cause liver disease in animals, with Hepatitis B virus (HBV) infecting humans. HBV is an enveloped virus with an approximate 3.2 Kb genome of a partially double stranded DNA chain and a single stranded fragment. HBV replicates through an intermediary RNA via a viral reverse transcriptase. The main target of infection by HBV is the hepatocyte and infection can occur through vertical or horizontal transmission starting in the first years of life or during adulthood.[74]

Chronic infection by HBV is one of the main causes of hepatocellular carcinoma (HCC). The carcinogenesis process triggered by HBV is complex, involving direct and indirect mechanisms with the latter being driven by chronic inflammation [75]. Direct mechanisms such as expression of viral oncogenes and insertional mutagenesis have also been documented [76]. HBV X (HBx) is the main oncogenic viral protein. HBx is a viral replication protein that participates in transcription and DNA repair through which it regulates cell cycle, apoptosis and genomic instability [77-78].

4.5.Hepatitis C Virus

Hepatitis C virus (HCV)is a member of the Flaviviridae family; there are at least six genotypes that are regionally distributed and divided into subtypes [79]. The HCV genome consists of a single strand RNA of positive polarity of approximately 9600 nucleotides from which a polyprotein is translated from an unique open reading frame and later subdivided into different viral polypeptides by viral proteases (reviewed in [80]). HCV infects hepatocytes causing an acute infection that may turn chronic when the immune system cannot eliminate it. In those cases, the carrier may progress to hepatitis, cirrhosis and eventually to HCC (reviewed in [80]). It is estimated that more than 170 million persons worldwide are infected by HCV from which about 40% will develop some form of liver disease and 1%–4% HCC [81]. Transmission commonly occurs through blood and infected blood products. Direct and indirect transforming mechanisms have also been described for HCV. The viral oncoprotein Core is the only viral product that in transgenic mice promotes the appearance of HCC [82]. Core is the main trigger of steatosis, an abnormal retention of lipids within the hepatocyte, and oxidative stress leading to chronic liver damage and HCC [83]. Different functions have been attributed to this protein, including altered cellular gene transcription, cell proliferation and cell death .[85-84]

4.6 .Human T-Lymphotropic Virus Type 1

The Retroviridae family groups several viruses with two copies of a positive sense single stranded RNA genome that is retro-transcribed to DNA and integrated into the host cell genome. Retroviruses are classified as simple and complex. Simple retroviruses encode gag, pol and env genes from which structural proteins are expressed, plus other proteins involved in viral replication and integration. Complex viruses encode additional regulatory genes besides the mentioned above.

HTLV1 is a potent direct carcinogenic agent that has been associated with a spectrum of lymphoproliferative diseases collectively referred as adult T-cells leukemia/lymphoma (ATL) [89]. HTLV1 is endemic of Japan, the Western African coast, Central America and the Caribbean, with 15–25 million people infected worldwide [90].

There are three demonstrated ways of transmission for HTLV1: sexual contact, intravenous and breast feeding. The virus infects T- and Blymphocytes and dendritic cells in vivo. Although, the main retroviral mechanism of transformation is by insertional mutagenesis, HTLV1 is a complex retrovirus whose genome also encodes the Tax oncoprotein. Tax has the ability to immortalize cells in vitro and its enforced expression in transgenic mice results in development of leukemia/lymphoma [91–95]. Tax is a transcriptional activator/repressor capable of modulating expression of multiple cellular genes and it also directly interacts with a plethora of cellular proteins. Tax principal mechanism of transformation is related to reprogramming cell cycle and inhibition of DNA repair [96].

Tax induces NFκB activity, which stimulates the expression of cytokines and their receptors, including those of IL-13, IL-15, IL-2, IL-2Rα and co-stimulatory surface receptors (OX40/OX40L) [97–99]. Importantly, this activity mimics the chronic inflammatory process critical in the oncogenic progression of many types of cancers. These molecules trigger T cell proliferation, which may help to amplify the pool of HTLV1 infected cells. Thus, contrary to other cancers in which the inflammatory process is mediated by immune cells in response to the oncogenic insult, in HTLV1 infection this is directly induced by Tax[96].

5 .Common Mechanisms of Direct Carcinogenesis

5.1. p53 and pRb

Inactivation and Other Targets of Increased Proliferation and Survival Viral oncogenes often increase the rate of cell proliferation and resistance to apoptosis, which eventually leads to alterations in DNA repair mechanisms and genomic instability. Increased mutation rates then alter cell polarity, with substrate independent growth, and acquisition of cell migration properties, among other malignancy-associated features. The mechanisms used by viruses to induce these cellular changes are similar and often converge on common signaling pathways and transcription factors. For instance, inactivation of p53 and pRb tumor suppressor genes is an event that occurs in most pathways of viral oncogenesis, both human and animal [100–102].

5.2 .Genomic Instability

Another common carcinogenic route promoted by infectious agents is genomic instability, which leads to gene amplification and deletion, changes in the number of chromosomes (polyploidy and aneuploidy) and aberrant fusion of non-homologous chromosomes (translocations). For instance, HPV-16 E6 and E7 proteins promote gene amplification, structural chromosomal alterations and centrosome replication errors leading to aneuploidy and polyploidy. Thus, HPV immortalized cell lines are characterized by gain and loss of whole chromosomes [130–133]. Increased rate of mutations are observed in the variable regions of heavy and light chains after EBV infection [136].

5.3 .Interfering with Telomere Shortening

Telomere shortening and cell senescence are the natural consequence of unlimited cell proliferation, and tumor viruses also display mechanisms of telomere maintenance. Telomere length maintenance is a fine regulated mechanism involving a complex set of proteins and the enzyme telomerase [143]. Expression of telomerase in physiological conditions is restricted to cells with stem properties, e.g., germinal cells or somatic stem/progenitor cells, but telomerase expression is turned off in differentiated cells. How tumor viruses regulate telomere length is not clear, but HPV E6, EBV LMP1, KSHV LANA, HTLV1 Tax and HBV HBx have all been shown to induce expression of telomerase [144–147]. Tumor viruses interference with DNA repair mechanisms and concomitant genomic instability may be in great measure a consequence of bypassing regulatory checkpoints of telomere length and p53- and pRb-dependent senescence[148]. In this scenario, tumor viruses have evolved with these mechanisms in order to achieve replicative immortality and thus persistency.

5.4. Viral miRNAs

MicroRNAs (miRNAs) have recently being shown to also participate in cell transformation. miRNAs are strongly conserved single stranded RNAs of approximately 22 nucleotide long that regulate expression of most genes. miRNAs inhibit mRNA translation mainly by translational repression based on base pair complementarity [157,158]. Almost all cancers present altered expression of cellular miRNAs [159,160]. However, a new and interesting topic in viral oncology concerns to viruses encoding miRNAs with oncogenic capabilities. The first five viral miRNAs were described in the EBV positive B95 cell line; to date, more than 40 miRNAs produced from the EBV BARTs and BHFR1 transcripts have been identified [161,162]. Those miRNAs are able to

inhibit apoptosis, and some target cellular tumor suppressor genes, such as: PUMA, Bin, TOMM22 and WIF1 [163–166]. EBV infection of gastric carcinoma cells (AGS) induced anchorage independence in absence of viral protein synthesis, highlighting the importance of EBV miRNAs in the malignant process [167].

6 .Common Mechanisms of Indirect Carcinogenesis

The mechanisms of indirect oncogenesis are more difficult to demonstrate since they cannot be measured by in vitro assays, nor the expression of viral genes in transgenic animal models recapitulates the oncogenic process.Besides chronic inflammation and immunosuppression (Figure 2), other proposed indirect mechanisms of transformation are described below (Figure 3).

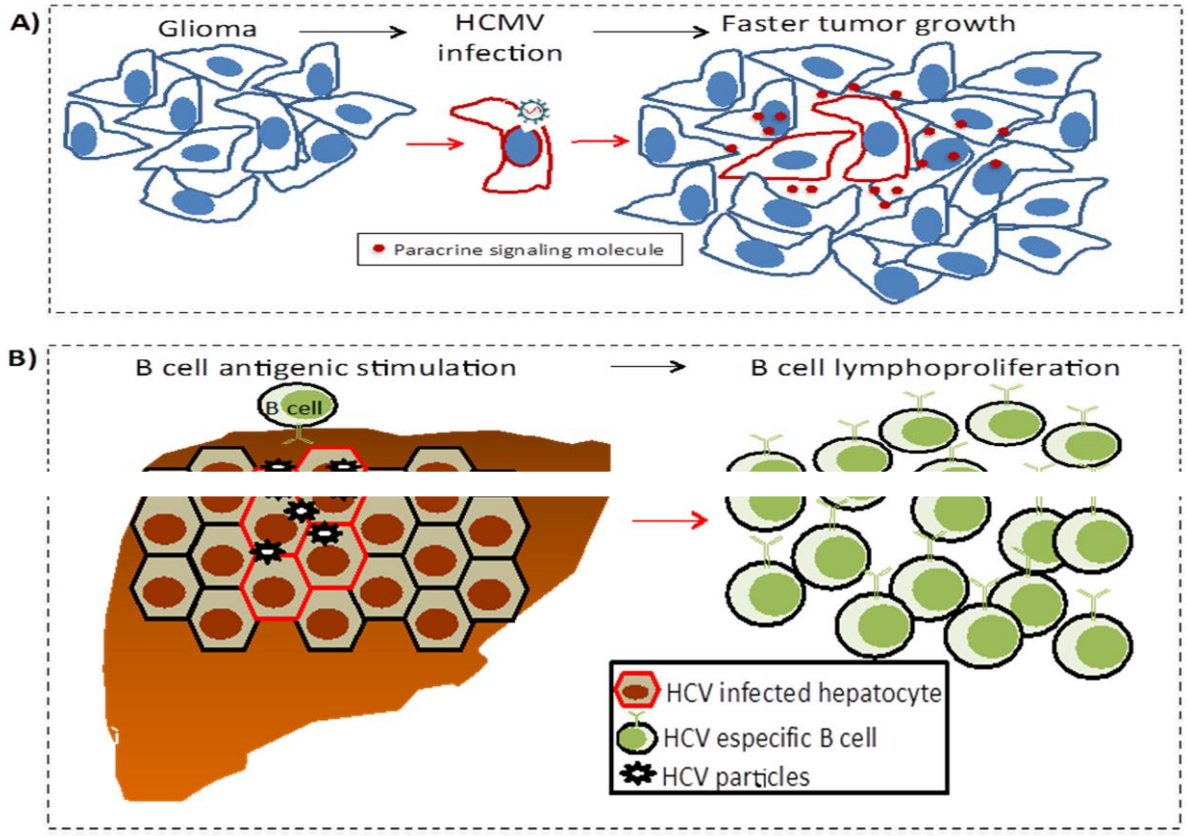

Figure 3. Other indirect mechanisms: Oncomodulation (A) and chronic antigen-driven lymphoproliferation (B). (A) In oncomodulation HCMV does not participate in the initial transformation of the glia; perhaps the virus has an increased tropism for tumor cells once the glioma has formed. Here, the virus only infects a fraction of the tumor cells activating signaling pathways that favor tumor growth; (B) B cells with antigen receptors specific for HCV antigens chronically respond to infected hepatocytes and free virus. This chronic stimulation increases the risk of unregulated lymphoproliferation and lymphoma.

6.1 .Chronic Inflammation

Persistent infection is generally accompanied by local chronic inflammation, still in the presence of evasion mechanisms of the immune response. It has been proposed that this chronic inflammation induces a constant and progressive local damage, closely associated to regeneration events of the damaged tissue. The inflammatory response is characterized by local expression of pro inflammatory cytokines, chemokines, adhesion molecules, growth factors and anti-apoptotic genes that regulate the sequential recruitment of leukocytes and stimulates fibroblasts and endothelial cells to divide and produce components of tissue remodeling and neovascularization [171].

A normal inflammatory response is self-limiting; chemoattraction of immune cells is gradually eliminated, pro-inflammatory cells already in the site of infection suffer apoptosis and are phagocytosed, while vascular changes are reversed. In contrast, in chronic inflammation associated with persistent infections, leukocytes remain in the lesion site and their apoptosis is suppressed. Additionally, to eliminate the infectious agent, immune cells produce oxygen and nitrogen free radicals, which are highly mutagenic. In this scenario, chronic inflammation favors the appearance of a cancerous clone, while tissue regeneration functions can also favor tumor growth, invasion and metastasis ([172], Figure 2A) .

HCV and HBV triggered inflammation correlates with necrosis and tissue regeneration that eventually progresses to hepatic lesions such as steatosis, fibrosis and cirrhosis, from which liver cancer emerges. It has been observed that during steatosis and fibrosis, the liver is highly infiltrated by immune cells and there is a microenvironment of inflammatory cytokines and chemokines, among which TGF-β and IL-1β stand out [180]. We have also observed that increased EBV reactivation correlates with severe gastric inflammation and increased tissue damage leading to advanced gastric lesions, arguing for an important role for inflammation in the EBV-associated transformation of the gastric mucosa .[181,182]

6.2 .Immunosuppression

The role of the immune system in onco-surveillance has been clearly established since the AIDS pandemic. Although, HIV is not capable of inducing tumors in its host cell, 40% of patients with AIDS develop cancers associated to the disease. Thus, severe immunosuppression induced by HIV infection indirectly promotes the development of tumors [17,183]. Individuals with a low CD8+ cytotoxic T lymphocyte count are more susceptible to infectious cancers [17],

such as EBV- and KSHV-associated lymphomas (exemplified in Figure 2B), KSHV sarcomas, HPV head and neck and cervical carcinomas, and MCPV Merkel cell carcinomas. Due to these features, HIV is classified as an indirect carcinogenic agent, while, direct transformation mechanisms mediated by EBV, KSHV, HPV and MCPV are still operating. [184].

7. Conclusions

Direct mechanisms infer expression of viral oncogenes together with deregulation of cellular oncogenes and/or tumor suppressor genes .

1-Among the most important indirect mechanisms are (i) the establishment of an inflammatory milieu in which chronic production of mutagenic molecules is persistently damaging the surrounding tissue, and (ii) immunosuppression with loss of the cancer immunosurveillance mechanisms. However, all tumor viruses probably present direct and indirect mechanisms of cell transformation .

2-Viruses importantly contribute with tumor initiation and progression. and HBV- and HCV-mediated liver cancer also progresses from a series of precursor inflammatory lesions besides their known capacity to express viral and cellular oncogenes .

3-The discovery of cancers with an infectious origin is critical to develop vaccines and preventive and therapeutic pharmacological therapies. This knowledge has already leaded to vaccines against HBV and high risk-HPV and targeted therapies against HIV and HCV.

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